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ANESTHESIOLOGY CLINICS OF NORTH AMERICA

19

Embolism I

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LEVON M. CAPAN, MD, and
SANFORD M. MILLER, MD, GUEST EDITORS

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to reduced cardiac output. In chronic embolic disease, the low mixed venous P_{O_2} plays the major role in the abnormal gas exchange. Other emboli, such as air, fat, and amniotic fluid, cause damage primarily by microvascular injury. In this setting, the clinical picture is much like that of the adult respiratory distress syndrome.

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Cumulative Index 1992 **905**

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FOREWORD

The differential diagnosis of a sudden cardiopulmonary arrest during anesthesia is not extensive; it includes massive exsanguinating blood loss, myocardial infarction, primary ventricular fibrillation/asystole, drug administration error (e.g., potassium, any overdose), and embolization to the pulmonary or coronary circulation. Thus, embolism during the perioperative period is one of the catastrophes with which anesthesiologists must be fully conversant. Because the subject is obviously of fundamental importance, has a clinically significant frequency, occurs in widely diverse clinical settings and operations, and has not been well covered in a clinically relevant manner in one text, we have decided to devote two issues of the *Anesthesiology Clinics of North America* to embolism and anesthesia. The first of the two issues, "Embolism I," covers the cardiopulmonary pathophysiology of embolism and the most common cause and form of embolism, namely, deep vein thrombosis and pulmonary thromboembolism. The second issue covers all of the other widely diverse kinds of embolism (air, fat, amniotic fluid, tumor, septic, foreign material, and therapeutic embolization).

The reason the topic of embolism and anesthesia is well covered in these issues of the *Anesthesiology Clinics* is because of the great expertise of the guest editors, Drs. Capan and Miller. Dr. Capan is an anesthesiologist with considerable surgical background. He has done much research and has published widely on thoracic and trauma anesthesia. Most significantly, Drs. Capan and Miller have edited a very well received and appreciated book *Trauma: Anesthesia and Intensive Care* of which nine chapters are authored by them. Dr. Capan is an excellent teacher, as evidenced by the fact that he has lectured and conducted workshops extensively on a national basis and has been voted teacher of the year twice by the anesthesia residents at the New York University School of Medicine. At Bellevue Hospital, Dr. Capan is Associate Director of the Department of Anesthesia, Medical Director of the Operating Room and Recovery Room, and Chairman of the Operating Room Committee. Dr. Miller, a full-time clinical anesthesiologist since 1960, has co-authored many of the contributions mentioned in connection with Dr. Capan. Dr. Miller is a prominent member of and has contributed extensively to the New York State Society of Anesthesiologists, including being a District President in 1984.

In summary, these two issues of *Anesthesiology Clinics of North America* on "Embolism and Anesthesia" are an extremely valuable contribution because of the importance of this subject, the fact that the topic has not been covered in one text until now, and the great wisdom and insight of the guest editors.

JONATHAN L. BENUMOF, MD
Consulting Editor

FORTHCOMING ISSUES

March 1993

EMBOLISM II

Levon M. Capan, MD, and Sanford M. Miller, MD,
Guest Editors

Embolism during anesthesia is one of the catastrophes with which anesthesiologists must be fully conversant. Because the subject is of fundamental importance, has a clinically significant frequency, occurs in widely diverse clinical settings and operations, and has not been well covered in a clinically relevant manner in one text, we have devoted two issues of the *Anesthesiology Clinics of North America* to the subject of embolism and anesthesia. These two unique issues, "Embolism I" and "Embolism II," cover the cardiopulmonary pathophysiology of embolism and all the possible forms of embolism (thrombus, air, fat, amniotic fluid, tumor, septic, and foreign material) in great breadth and depth in a clinically relevant manner. The quality of these two volumes of the *Anesthesiology Clinics* is guaranteed because of the great clinical wisdom and insight of the guest editors, Drs. Capan and Miller.

June 1993

NEUROMUSCULAR FUNCTION AND BLOCKADE

Brian L. Partridge, MD, *Guest Editor*

September 1993

ANESTHESIA FOR EAR, NOSE, AND THROAT SURGERY

Mitchell B. Sosis, MD, PhD, *Guest Editor*

RECENT ISSUES

September 1992

CEREBRAL PROTECTION, RESUSCITATION, AND MONITORING

Bruno Bissonnette, MD, *Guest Editor*

June 1992

CURRENT CONCEPTS IN ACUTE PAIN CONTROL

Alan N. Sandler, MB, ChB, *Guest Editor*

March 1992

EPIDURAL AND SPINAL ANALGESIA AND ANESTHESIA:
CONTEMPORARY ISSUES

M. S. Batra, MD, *Guest Editor*

PREFACE

LEVON M. CAPAN, MD SANFORD M. MILLER, MD
Guest Editors

Embolic phenomena have attracted the interest of various medical specialists throughout the years. Anesthesiologists, by virtue of their involvement with the care of a broad spectrum of patients in a variety of clinical settings, are often confronted with the need to manage embolic complications. Many surgical procedures carry a high risk of embolism. Hip and knee joint replacement surgery and neurosurgical procedures in the sitting position are two of the more familiar examples, but they are by no means the only ones. In addition, the risk of embolism is an ever present consideration preoperatively, taxing the diagnostic and preventive capabilities of the anesthesiologist. Management of this complication is also of great importance to the intensivist in the critical care and recovery units. Thus, this subject has broad applicability to practitioners of our art and science.

Although there is a fair amount of information about *air embolism* in the anesthesia literature, little is written concerning specific management of other types of emboli. Furthermore, to the best of our knowledge, no anesthesia text has so far been devoted specifically to the subject of embolism *per se.* The current and forthcoming issues of the *Anesthesiology Clinics of North America* address that deficiency, and present a summary of the available information on embolic phenomena under one heading in a form intended to meet the needs of the anesthesia community.

The current issue is divided into five articles. The first three represent basic knowledge and provide information about the overall pathophysiology of embolism in considerable detail. Pulmonary and cardiovascular effects of embolism are each discussed separately, while considering the interrelation between the two. The third article is devoted to the interatrial septum and its abnormalities. Advances in the field of echocardiography have increased our understanding of the importance of the septum in systemic embolism, justifying a separate review of this topic. The fourth and fifth articles discuss thromboembolism, the most common type of embolism and the subject of a substantial amount of research during the past 20 years.

Relatively few of our references are from the anesthesia literature, because, as we have noted, it contains a paucity of information on embolic phenomena. Some of the recommendations for anesthetic and intensive care are drawn, of necessity, from anecdotal reports or from the authors' personal observations and experience. Contributors to this issue, however, are well qualified to make such recommendations, having been selected for their participation in important research work in the area and their expertise in managing patients with embolic complications. Nevertheless many questions remain unanswered. We hope that the present work will stimulate attempts to answer some of these.

We would like to thank all of the authors for contributing generously of their time and knowledge in the preparation of this publication. We would like to acknowledge in particular Helaine Barron, editor of the *Anesthesiology Clinics of North America,* for her assistance, support, and stimulating remarks about the publication of this issue. We also thank our Department Chairman, Herman Turndorf, MD, for his constructive criticism and support in preparing this volume, as he has traditionally given for the past 20 years. We are grateful to our administrative secretary Christine Woolever for her willing and cheerful performance of the many tasks essential to the success of this venture. Finally and most importantly, we thank our families, Ani and Natalie Capan, and Marcia, Kevin, Douglas, and Diane Miller; not only for their tolerance, but for making it all worthwhile.

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CARDIOVASCULAR PERFORMANCE IN EMBOLISM

David J. Dries, MD, and Mali Mathru, MD

OVERVIEW

Vascular Bed

Pulmonary thromboembolism is a major clinical problem that contributes to over 150,000 deaths per year in the United States. Symptomatic pulmonary emboli are fatal in approximately 10% of cases; approximately half of these deaths occur within the first hour, usually due to massive occlusion of the main pulmonary artery or its branches. In this situation there is little time to establish the diagnosis and institute appropriate therapy. Dalen and Alpert[11] estimated that in more than two-thirds of patients surviving the first hour, the diagnosis of pulmonary thromboembolism is not made, treatment is not instituted, and mortality approaches 30%. In patients whose pulmonary thromboembolism is diagnosed and treated with anticoagulants or lytic therapy, mortality is only 5% to 10%.[11] An even lower death rate (2.5%) has been reported recently for properly diagnosed and treated patients; the recurrence rate was 8.3% in the survivors, of whom 45% died within 1 year.[8a]

The majority of pulmonary emboli originate in the deep venous system of the lower extremities or pelvis. Symptoms or signs of phlebitis in the lower extremity are present in only 50% of these patients, however (see article by Kaufman). Thrombi may also arise from the right atrium or ventricle in the presence of biventricular heart failure. Right ventricular mural thrombi are seen in up to one-third of patients

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with a pulmonary artery catheter. The importance of catheter-related mural thrombi in the etiology of pulmonary embolism remains unclear.[17, 77]

Common risk factors for pulmonary thromboembolism include a previous history of embolism, congestive heart failure, surgical or other trauma, and malignancy. In the pulmonary circulation, large clots may lodge at bifurcation points in the pulmonary and lobar arteries, usually causing hemodynamic compromise. Smaller clots may propagate distally to the arterioles. The lower lobes are involved more often than the upper, and emboli are frequently multiple. Only 15% of pulmonary emboli cause pulmonary infarction, usually in patients with preexisting cardiopulmonary disease[77] (see article by Dehring).

Most pulmonary emboli appear to be silent. When clinically apparent, the presentation most suggestive of this diagnosis is acute, otherwise unexplained dyspnea. Symptoms and signs correlate to some degree with the size of the embolized material. Small to medium clots usually cause pulmonary symptoms, including dyspnea, chest discomfort, and cough. Tachypnea and tachycardia are present in the majority of patients. Mild fever is also common. Hemoptysis, pleural pain, and a friction rub indicate pulmonary infarction. Massive pulmonary embolism, defined as obstruction of two or more lobar vessels or their equivalent at the segmental level, often produces cardiovascular manifestations, including syncope, chest pain, dyspnea, and cough, along with signs of right ventricular dysfunction: right ventricular heave, right ventricular S-3, jugular venous distension, and a murmur of tricuspid regurgitation.[3, 77]

The consequences of acute obstruction of the pulmonary arterial tree result from the physiologic features of the pulmonary circulation. The normal mean pulmonary arterial pressure, about 12 to 15 mm Hg, is one-sixth to one-eighth of the systemic pressure. With a high flow and a pulmonary venous pressure of about 8 mm Hg, the pulmonary vascular resistance is normally about one-tenth of that of the systemic circulation.[61] Acute reduction in the pulmonary vascular cross-sectional area by obstruction of the pulmonary arterial circulation creates a sudden increase in output load on the right heart chambers, leading to right heart failure.[58] Subsequent hemodynamic consequences are secondary to this, although other mechanisms may also play a role. Reduction in the patent vascular bed results in an immediate increase in pulmonary vascular resistance, and if cardiac output is to be maintained, an increase in pulmonary artery pressure and right ventricular work is mandatory. The normal pulmonary vascular reserve capacity is such that about 50% of the cross-sectional area must be lost before sustained pulmonary hypertension is seen at normal levels of cardiac output.[6] The greater the degree of occlusion, the higher will be the pulmonary artery pressure.[50] The ability of the right ventricle to compensate for embolic occlusion is limited. Several studies suggest that in patients without prior cardiopulmonary disease, the maximum attainable mean pulmonary artery pressure is approximately 40 mm Hg.[14, 50, 53] The dilatation of a previously normal right ventricle at this level of pressure may result in acute tricuspid regurgitation. If this load is sustained, cardiac output may fall and acute cor pulmonale and shock may ensue. Mean pulmonary artery pressures greater than 40 mm Hg suggest the presence of previous pulmonary emboli or underlying cardiopulmonary disease.[82]

The extent of embolic occlusion is only one of the three major determinants of the severity of the hemodynamic consequences of pulmonary embolism. The other two are the cardiovascular status of the patient before embolization and the activity of reflex and humoral factors. Although the latter factors play a role in determining the severity of hemodynamic response to embolism in experimental animals, their role in humans is less clear.[32, 76, 82]

The respiratory consequences of pulmonary embolism include an increase in alveolar dead space.[12] In addition, surfactant loss and hypoxemia resulting from ventilation/perfusion inequality with intrapulmonary shunting are noted. Mixed venous oxygen tension is decreased as a result of reduced cardiac output.[58, 82] In addition to vascular bed changes, shortening of terminal bronchioles and alveolar ducts has been noted, decreasing the volume of the lung. This effect may be caused by contraction of longitudinal smooth muscle fibers in terminal airways triggered by low carbon dioxide tension in the embolized area.[59] In the cardiovascular changes, circulating humoral agents, including serotonin, histamine, and prostaglandins, seem to play a role in experimental animals, but these effects have not been documented in patients. Later changes after embolism include loss of surfactant activity with development of atelectasis and transudation of interstitial fluid into the alveolar space[21] (see also article by Dantzker).

Right Ventricular Performance in Pulmonary Embolism

With acute increases in pulmonary vascular resistance, the thin-walled compliant right ventricle decompensates.[7, 33, 80] Massive pulmonary embolism dramatically increases the right ventricular afterload, enlarges the ventricle, and shifts the ventricular septum to the left. Echocardiographic studies demonstrate this septal shift and the resultant decreased left ventricular volume.[61] These changes thus decrease left ventricular compliance and ultimately limit cardiac output.[13]

The coronary perfusion pressure of the right ventricle is reduced by the low systemic blood pressure and the increase in right ventricular end-diastolic pressure. Coronary flow to the right ventricle may also be limited by distension of the chamber. In acute right ventricular distension, coronary flow may occur only in diastole instead of throughout the cardiac cycle. The increased work load seen by the right ventricle, in association with this decrease in blood supply, creates ischemia, which further decreases the right ventricular ejection fraction, causing additional right ventricular distension and further compromise of the function of the left ventricle.[7, 33] Further right ventricular decompensation occurs if elevated right atrial and ventricular pressures cause flow through a patent foramen ovale or an incompetent tricuspid valve.[58]

Right ventricular function is difficult to assess because the chamber is crescent shaped and posterolateral in location. Right ventricular ejection fraction and stroke volume may be calculated utilizing pulmonary artery catheters with rapid-response thermistors that measure beat-to-beat temperature variations.[39] Studies on normovolemic goats suggest that right ventricular ejection fraction (RVEF) is decreased from 51% to 26% following pulmonary microembolization. Treatment with inotropic, pressor, and vasodilator agents may increase RVEF to approximately 40%.[46] Techniques available to assess right ventricular function clinically include echocardiography, digital subtraction angiography, and radionuclide angiography with single or multiple evaluations. However, these measurements are not easily derivable, are difficult to perform on a sequential basis, or may require movement of a critically ill patient to the location of the necessary equipment.

Hemodynamic findings after pulmonary embolism are nonspecific. With large emboli, the cardiac output is low and the right ventricular diastolic and mean atrial pressures are generally elevated.[53] The pulmonary artery pressure tends to be increased but correlates poorly with the size of the embolus in patients with underlying cardiovascular disease. In patients without underlying cardiovascular disease, the pulmonary artery pressures may be normal even in the presence of massive embolism.[52] Electrocardiographic changes include nonspecific ST segment and T wave changes. In many patients, these findings may represent underlying ischemic heart disease or chronic obstructive pulmonary disease.

THE RIGHT VENTRICLE

Right Ventricular Anatomy/Physiology

The last two decades have seen a renewal of interest in the right ventricle. This thin-walled chamber has long been obscured by its more muscular neighbor on the left side. The renewed interest in the right ventricle is an outgrowth of an evolving awareness that dysfunction of this chamber plays a critical role in several frequently encountered, clinically important cardiopulmonary disorders, including pulmonary thromboembolism.

In an adult, the normal right ventricle is crescent shaped with compliant walls. Because of a large surface-to-volume relationship, the right ventricle serves to propel large amounts of blood into the pulmonary artery with minimal myocardial fiber shortening. The right ventricle is unable to generate high intracavitary pressures. Normally, the right ventricle functions as a low-pressure volume conduit ejecting venous blood into the high-compliance, low-resistance pulmonary vascular bed.[84]

The left ventricle has less compliant walls than the right ventricle and a much smaller surface area-to-volume ratio. This chamber generates high pressures through contraction and relaxation of circumferential muscle bundles. The left ventricle sustains stroke volume in the presence of elevated systemic arterial pressures but is less suited than the right ventricle to handle increases in volume. The systolic performance of both ventricles is determined by the same three factors: preload, afterload, and contractility.[48, 68] End-diastolic pressure represents the ventricular preload, whereas afterload is the resistance seen by the ventricle during contraction. Arterial pressure and vascular resistance are the commonly used indices of afterload. However, ventricular wall tension related to the product of chamber diameter and ventricular pressure is a more precise estimate of afterload. Augmentation of diastolic volume increases both preload and afterload. The vigor of muscle shortening occurring at any given preload and afterload is called myocardial contractility. The Frank-Starling relationship provides a framework for assessment of left and right ventricular performance.[68] Ventricular function curves relate systolic pump function to preload and contractility.

It is important to note that qualitative differences exist between the left and right ventricles. For instance, the right ventricle is unable to maintain its ejection fraction when faced with an elevated afterload. Thus, augmenting preload is necessary to preserve the stroke volume of the right heart in the presence of pressure stress. This volume compensation is less important when the normal left ventricle is confronted by afterload elevation, probably as a result of the increased contractile reserve of this chamber.[48]

The free wall of the right ventricle is perfused almost entirely by the right coronary artery.[20] The interventricular septum is supplied by both the left anterior descending coronary artery and the right coronary artery. As noted by Matthay and associates,[48] the total blood flow to the left ventricle is considerably greater than that of the right. The flow of blood per gram of tissue in the right ventricle is only about two-thirds that perfusing the left ventricle, and the right ventricle contains less muscle. The left ventricle also extracts more oxygen per gram of tissue than the right. In contrast to the left ventricle, blood flow to the myocardium of the right ventricle is distributed more evenly throughout the cardiac cycle,[44] presumably as a result of the high pressures developed by the left ventricle during systole; thus, perfusion occurs primarily during diastole. The driving pressure for perfusion of the right ventricle is aortic pressure minus right ventricular pressure. Systemic hypotension in association with left ventricular failure, therefore, results in right ventricular ischemia and abnormal contraction. In addition, an increase in right ventricular pressure, caused by increased afterload, may also reduce right coronary blood flow. This, in turn, limits the ability of the right ventricle to respond to increased pressure demands.[48]

Matthay and associates[48] describe the response of the right ventricle to stress as a vicious cycle leading to circulatory collapse if the insult is sufficiently severe. Right coronary blood flow increases to meet mild or moderate pressure loading of the right ventricle despite the decrease in driving pressure, because the vessel dilates and resistance to flow decreases.[45] Augmentation in preload also serves to maintain right ventricular systolic function. However, this adaptation is limited, because increasing right ventricular volume is associated with increased wall tension (and oxygen demand), decreased left ventricular compliance, and tricuspid regurgitation. These factors may decrease aortic pressure and cardiac output, reducing right coronary perfusion pressure, whereas increasing the demand for oxygen by the myocardium. When right coronary vasodilatory reserve is exhausted, myocardial ischemia results and right ventricular systolic function is lost. At this point, unless the right ventricle is resuscitated, circulatory collapse will follow[48, 80] (Figs. 1 and 2).

Wiedemann and Matthay define right ventricular failure as the point at which the systolic function of this chamber is inadequate to maintain adequate circulation.[48, 84] In the face of even moderate pressure stress, right ventricular preload increases and ejection fraction decreases. Peripheral edema may be a manifestation of the increased mean right ventricular pressure with resultant elevation of right atrial pressure.[75] Under these circumstances, right ventricular contractile function may still be normal. The variety of clinical manifestations of right heart stress, which have been discussed previously, is determined by the interaction between the cause of the dysfunction and the intravascular volume status. Invasive hemodynamic monitoring may be misleading in this setting. Right ventricular decompensation in a previously normal chamber may not be associated with a high right atrial pressure despite a large ventricular volume, primarily because of the high compliance of the normal right ventricle. On the other hand,

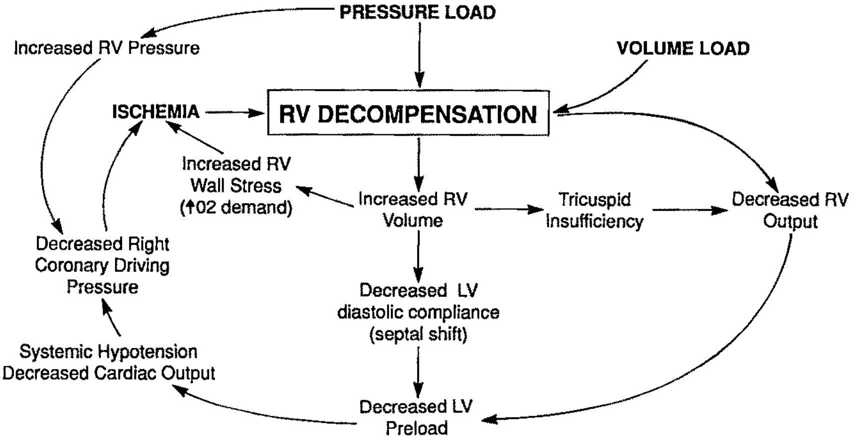
PRESSURE LOAD
Increased RV Pressure
VOLUME LOAD
ISCHEMIA
RV DECOMPENSATION
Increased RV Wall Stress (↑02 demand)
Increased RV Volume
Tricuspid Insufficiency
Decreased RV Output
Decreased Right Coronary Driving Pressure
Decreased LV diastolic compliance (septal shift)
Systemic Hypotension Decreased Cardiac Output
Decreased LV Preload

Figure 1. The pathophysiology of acute right ventricular failure (the "vicious cycle") is schematically depicted. (*From* Wiedemann HP, Matthay RA: Acute right heart failure. Crit Care Clin 1:631–661, 1985.)

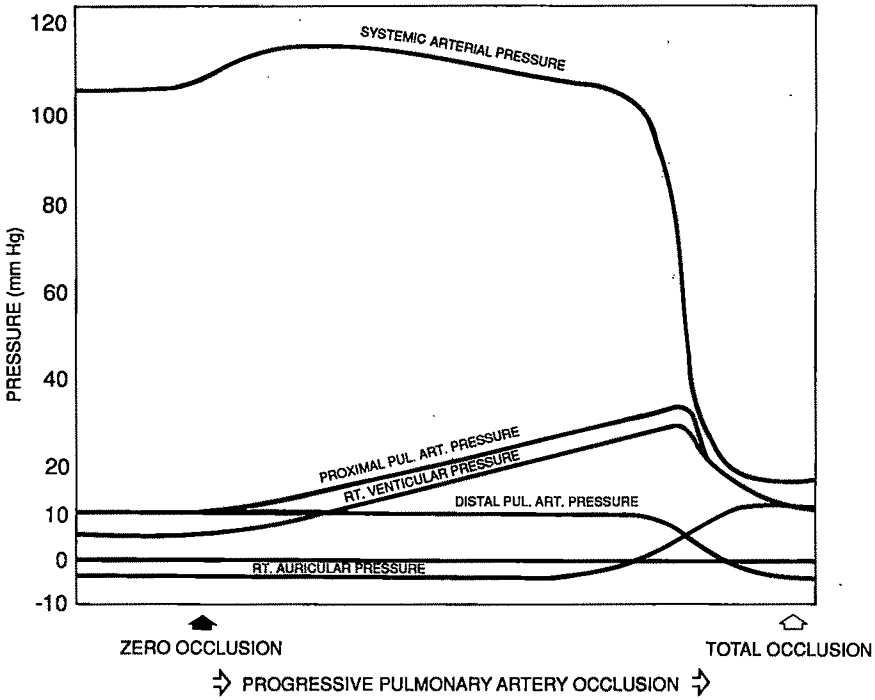

Figure 2. Mean pressures observed as the main pulmonary artery of the dog was progressively constricted over a 4- to 5-minute period. The right ventricle was unable to generate a pulmonary artery pressure greater than 40 mm Hg, and circulatory collapse suddenly occurred. (*From* Guyton AC, Lindsey AW, Gilluly JJ. The limits of right ventricular compensation following acute increases in pulmonary circulatory resistance. Circ Res 2:326–332, 1954; by permission of the American Heart Association.)

a chronically hypertrophied right ventricle may exhibit high diastolic pressures while normal circulation is maintained. In addition, owing to the phenomenon of ventricular interdependence, left ventricular dysfunction, as suggested by a high wedge pressure in the absence of left ventricular disease, may be a manifestation of right ventricular failure.

Right Ventricular Resuscitation

If right ventricular outflow is diminished as a result of increased right ventricular afterload or depressed contractility, cardiac output can be restored by volume expansion. This has been shown in several situations, including the adult respiratory distress syndrome (ARDS), right ventricular infarction, and acute pulmonary artery constriction.[9, 33, 71] Factors contributing to this improvement can be seen in the relationship between cardiac output and venous return (Fig. 3). An augmented venous volume causes a rightward shift in the venous return curve, thus compensating for diminished cardiac output. How-

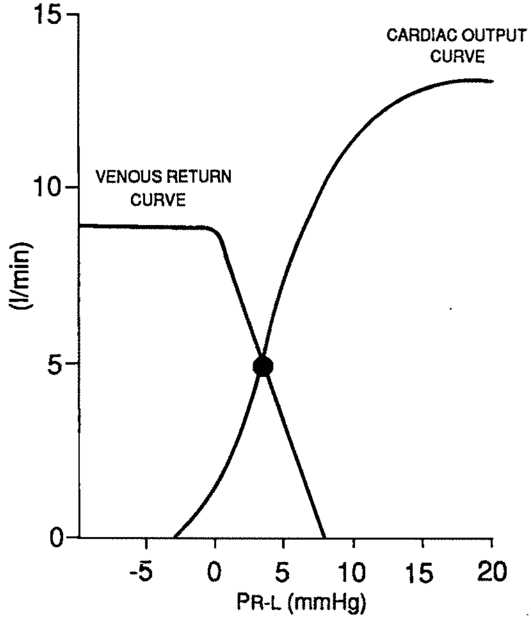

Figure 3. Blood flow is determined by the intersection of the venous return curve and the cardiac output curve. The cardiac output curve describes the function of the heart as a pump. The venous return curve is determined by the compliance, volume, and resistance of the vasculature. P_{R-L} represents the average filling pressure of the ventricles. (*From* Sylvester JT, Goldberg HS, Permutt S: The role of the vasculature in the regulation of cardiac output. Clin Chest Med 4:111–126, 1983.)

ever, it should be noted that systemic mean pressure rises with venous volume expansion, favoring the development of peripheral edema, and cardiac output may fall if the clinician administers a diuretic in an attempt to reduce or eliminate edema. Thus, it may be necessary to accept peripheral edema in order to maintain cardiac output in patients with compromise of right ventricular function.[75]

There is a clear limit to the ability of increased right ventricular preload to maintain cardiac output. A decrease in left ventricular diastolic filling and tricuspid regurgitation may develop following volume loading to optimize right ventricular function. In addition, an increase in circulatory volume may cause a rise in wall tension and increased oxygen demand even though the compliance of the right ventricle is high. Right coronary perfusion pressure is also reduced by the high systolic pressure generation required to overcome increased right ventricular outflow resistance.[64, 65] In patients with ARDS, volume loading may be associated with worsening pulmonary edema if the right ventricular volume is raised to the degree that left ventricular compliance is reduced and pulmonary capillary wedge pressure is elevated. The point beyond which further volume loading is detrimental to right ventricular function is indicated by a precipitous rise in left- or right-sided filling pressures without a concomitant increase in cardiac output.[65]

Maintenance of aortic pressure is critical to continued adequate right coronary artery perfusion and avoidance of myocardial ischemia with the onset of acute right ventricular failure. Thus, therapy for acute right ventricular failure may at times include intra-aortic balloon counterpulsation, aortic banding, or phenylephrine or norepinephrine infusion. Although right ventricular performance may be directly improved by pressors, the common mechanism in each of these therapies is an augmentation of aortic pressure.[48, 64, 65]

A practical means of rapidly lowering afterload stress in acute right ventricular failure is oxygen therapy. As hypoxic pulmonary vasoconstriction contributes to elevated pulmonary vascular resistance in many patients with chronic obstructive pulmonary disease (COPD), ARDS, pulmonary thromboembolism, and interstitial lung disease, supplemental oxygen may lower pulmonary vascular resistance and pulmonary artery pressures when these disorders are associated with hypoxemia. Right ventricular ejection fraction may also be increased by oxygen therapy.[24]

The therapy for pulmonary arterial hypertension with vasodilators has produced conflicting and confusing results. A beneficial hemodynamic response to these agents has not been clearly defined. This is in part due to the fact that pharmacologic agents may have several sites of action—in some cases altering ventricular contractility and preload. Other agents, such as selective β_2-adrenergic agents, may decrease air flow obstruction and reduce pulmonary vascular resistance by this effect as well as by direct pulmonary vasodilation. However, some vasodilator agents may produce a decrease in arterial oxygen tension by increasing physiologic shunting and ventilation perfusion mismatch within the lung. The primary risk in administering pharmacologic vasodilators to reduce right ventricular afterload is the potential for adverse effects on the systemic circulation. Patients with fixed low cardiac output due to right ventricular decompensation may be further compromised by systemic vasodilation associated with hypotension and the resultant loss of right coronary artery perfusion pressure. This may be the mechanism of deaths reported after administration of hydralazine or diazoxide to patients with severe pulmonary artery hypertension.[48, 62, 67, 84] The underlying disease process may also affect the results of vasodilator therapy in the pulmonary circulation. The effects of specific agents will be discussed later in this article.

Finally, experimental work with acute pulmonary thromboembolism suggests that balloon counterpulsation may be successfully applied to the pulmonary circuit. Pulmonary artery counterpulsation reduces impedance to right ventricular outflow but does not directly augment coronary artery flow as does aortic counterpulsation. In canine models, pulmonary artery counterpulsation reverses cardiogenic shock by increasing right ventricular work and decreasing right ventricular end-diastolic pressure. In humans, this technique requires insertion of a conventional intra-aortic balloon into a Dacron sleeve sewn to the side of the main pulmonary artery.[23, 47, 57, 60]

The final means of right ventricular resuscitation is augmentation of contractility. This can be achieved by using adrenergic agents, including dobutamine, dopamine, norepinephrine, and isoproterenol. All of these drugs increase right ventricular contractility.[20, 64, 65] Inotropic agents may produce minimal improvement of right ventricular performance if afterload is normal owing to the normally steep slope of the right ventricular systolic function curve. The value of catecholamines in treating acute right heart failure secondary to increased pulmonary vascular resistance is suggested by the work of Prewitt and associates.[64–66] Their studies, limited to anesthetized and ventilated dogs, suggest that as pulmonary vascular resistance is gradually raised with glass bead embolization, right ventricular afterload increases and cardiac output falls. Volume expansion is successful in improving cardiac performance in the early stages, but after a certain point cardiac output deteriorates with further volume administration. These investigators then noted enhanced right ventricular performance and cardiac output with the administration of dopamine or norepinephrine.[64, 65] Other agents, including albuterol, terbutaline, and theophylline, may improve right ventricular contractility. There are few data available to support a consistent pattern for the use of these drugs.[48]

Right ventricular contractility is increased by digitalis and other cardiac glycosides.[72] However, it is difficult to say whether these agents should be used, since digitalis may exhibit adverse effects on right ventricular function as a result of pulmonary vasoconstriction. In addition, cardiac glycosides may cause a shift in the venous return curve to the left and thus adversely affect cardiac output.[75] Several authors suggest that unless coexisting left ventricular dysfunction is present, digitalis does not appear to relieve right ventricular dysfunction.[75] Digitalis augments right heart function in the presence of left ventricular failure by reducing pulmonary venous pressure and right ventricular afterload. In the absence of left heart disease, no overall improvement and possible deterioration in right ventricular function may result from digitalis administration. Thus, Matthay and associates recommend against the use of digitalis for acute right heart failure unless coexisting left ventricular failure is present.[48, 84]

Right Ventricular Function in Pulmonary Embolism

To summarize the previous discussion, the thin-walled compliant right ventricle decompensates with acute increases in pulmonary vascular resistance.[7, 13, 33, 80] Massive pulmonary thromboembolism dramatically increases right ventricular afterload, enlarges the right ventricle, and shifts the ventricular septum to the left, resulting in a decreased left ventricular volume.[61] Left ventricular compliance and output are also diminished (Fig. 4). Coronary perfusion pressure of the right ventricle is reduced by both low systemic blood pressure and high right ventricular end-diastolic pressure.[7] Right ventricular distension may

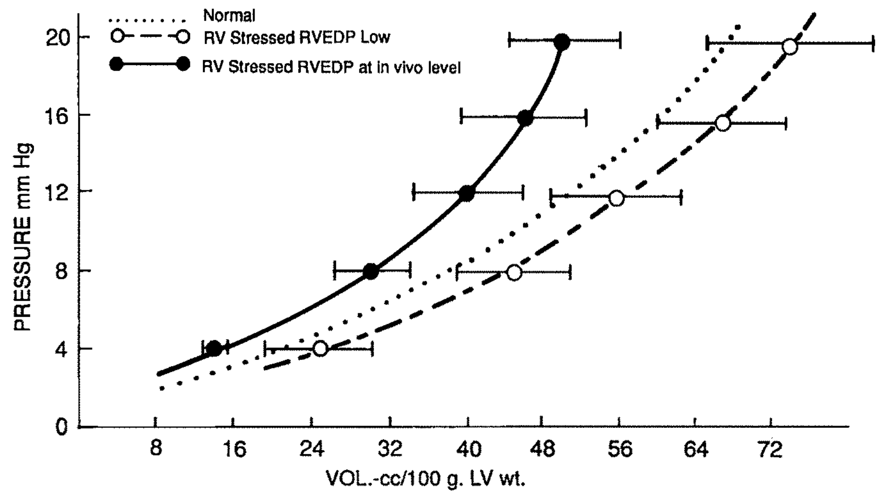

Figure 4. The left ventricular (LV) diastolic volume-pressure curve is shown in three groups of dogs: normal; dogs with right ventricle pressure stress, in which right ventricle end-diastolic pressure (RVEDP) is kept at the low levels found in normal animals; and dogs with right ventricle pressure stress in which the RVEDP is allowed to reach higher levels. This illustrates ventricular interdependence whereby right ventricular stress decreases left ventricular compliance. (*From* Kelly DT, Spotnitz HM, Beiser GD, et al: Effects of chronic right ventricular volume and pressure loading on left ventricular performance. Circulation 44:403–412, 1971; by permission of the American Heart Association.)

allow coronary flow only in diastole instead of both systole and diastole. The ejection fraction is decreased by the resultant ischemia that leads to increasing ventricular dilation. The additional right ventricular dysfunction further affects the performance of the left ventricle.[84] Volume loading in order to augment right ventricular performance may compromise its function when increased afterload secondary to thromboembolism cannot be overcome. Ischemia may also result from decreased right coronary driving pressure or systemic hypotension related to decreased cardiac output. In this setting, an increased right ventricular wall tension increases myocardial oxygen demand at the same time that the forces previously described tend to reduce right ventricular coronary flow. As described by Matthay and associates, increased right ventricular volume may also create tricuspid regurgitation, which also serves to decrease right ventricular output.[48, 84] Increased right ventricular wall stress and demand for coronary blood flow constitute a potential source of ischemia in older individuals with silent right coronary heart disease. In these patients, the demand for right ventricular perfusion may not be met unless coronary artery perfusion pressure is high. We must also note that both the right and left ventricles reside within a pericardial sac with limited compliance. Thus, as right ventricular size increases with initial intravascular volume therapy, large changes in intravascular volume may be accompanied by minimal changes in ventricular filling pressures until the limits set by the pericardium are reached. At this point, right- and left-sided filling pressures may equalize and biventricular failure ensue.[42]

Obstruction of the pulmonary vascular bed is not the only cause of pulmonary arterial hypertension following thromboembolism. Pulmonary artery pressures may be elevated when more than 30% of the vascular bed is occluded with emboli even though it has been stated that, in normal individuals, at least 50% of the lumen of the pulmonary artery must be occluded before an increase in resting pulmonary artery pressure is noted.[51] Therefore, neurogenic and humoral mechanisms must also be operative. As noted above, the maximal mean pulmonary artery pressure achievable by the normal heart in the presence of acute massive pulmonary artery occlusion is approximately 40 mm Hg. Increased right ventricular outflow resistance at this point may lead to rapid dramatic hemodynamic collapse or death if even a relatively mild reembolization occurs.[33, 51]

If there is preexisting cardiopulmonary disease, the response to pulmonary thromboembolism may be modified. With right ventricular hypertrophy, mean pulmonary artery pressures greater than 40 mm Hg may be generated. In addition, the pressure begins to rise from the pre-embolic baseline value at a lesser degree of embolic vascular occlusion. On the other hand, a more dramatic reduction in cardiac performance following any degree of pulmonary vascular occlusion is noted in patients with congestive failure or other cardiopulmonary anomalies.[48]

Impact of Therapy on Right Ventricular Performance in Pulmonary Thromboembolism

Acute right ventricular hypertension may be studied by constriction of the main pulmonary artery until the right ventricle fails. The implications of vascular constriction are discussed below. Here we will relate the impact of acute pressure loading by thromboembolism on right ventricular function and the impact of various therapeutic interventions on the acute compromise of right ventricular performance that may occur in this setting.

Ischemia of the right ventricular free wall may be the limiting factor in response of this chamber to an acute pressure load. As it develops, ischemia may initiate a cycle of rapid decompensation. This contrasts with the fact that when pulmonary outflow is normal, ischemia of the right ventricle has little impact on circulatory function. Acute occlusion of the right coronary artery in canine models results in reduced right ventricular response to pressure loading[7]: these animals exhibit a more rapid fall in cardiac output and aortic pressure, with a more rapid rise in right ventricular end-diastolic pressure, than do normal animals. Increasing right coronary artery perfusion pressure may reverse right ventricular decompensation. Improvement in right ventricular performance was also achieved by increasing aortic root pressure with mechanical distal aortic obstruction.[74] This effect was presumably also the result of augmented right coronary perfusion.

An additional compensatory mechanism was noted in studies with pigs. Right coronary vasodilation develops under conditions of right ventricular loading. Manohar and associates[45] demonstrated an increase of 91% over control valves in total blood flow to the right ventricular free wall in response to pulmonary artery constriction. Infusion of adenosine, a coronary vasodilator, also increased right coronary flow and improved right ventricular systolic pressure in animals so treated. Right ventricular systolic pressure increased even though mean aortic pressure decreased, causing a decrease in right coronary driving pressure. Thus, this work suggests that coronary vasodilator reserve remains intact during right ventricular pressure loading. This work was subsequently confirmed by other investigators.[22, 80] It should be noted that right coronary vasodilation is a limited phenomenon. With progressive pulmonary artery constriction, myocardial ischemia and the loss of coronary vasodilator reserve can be demonstrated. In this setting, myocardial performance can again be improved by increasing central aortic pressure and, thus, right coronary driving pressure.

Controlled administration of fluids, usually colloid solutions, improved hemodynamic response and tissue oxygenation in patients with pulmonary thromboembolism.[34, 61] Volume infusion should be titrated to a central venous pressure (CVP) less than 12 to 15 mm Hg and stopped if a large increase in CVP occurs. Fluid boluses may induce hemodynamic collapse in patients critically ill with pulmonary embolism. Laver and associates[42] describe the phenomenon of left ventricular end-diastolic tamponade secondary to right ventricular filling of the available pericardial space with resultant impedance of left ventricular function. Inappropriate volume administration may drive this effect. Fluid infusion also caused detrimental effects in dogs with right ventricular failure from microemboli or autologous clot infusion. Administration of boluses of dextran increased end-diastolic pressures and contributed to the deaths of all of the affected animals. Myocardial decompensation was related to increased oxygen consumption of the right ventricular free wall secondary to increased tension and inadequate coronary perfusion pressure.[26, 56]

Isoproterenol is an inotrope, pulmonary vasodilator, and bronchial dilator. Despite obvious theoretical advantages, isoproterenol appears detrimental in severe cases of clinical and experimental pulmonary embolism. In patients with minimal hemodynamic compromise secondary to pulmonary embolism, cardiac output and heart rate may be increased by administration of this agent. Mean blood pressure decreases. In the presence of more severe hemodynamic compromise, changes in cardiac index are small and the fall in blood pressure is more pronounced. Systemic vasodilation, excessive tachycardia, and arrhythmias may complicate the administration of isoproterenol. Hemodynamic collapse and death have been demonstrated following isoproterenol infusion in dogs with severe right ventricular failure secondary to autologous clot embolization.[13, 56]

Dobutamine and dopamine have been evaluated in a small group of unstable patients with pulmonary thromboembolism and no preexisting cardiopulmonary disease. After initial volume loading to a CVP of 13 mm Hg, dobutamine infusion increased cardiac index and reversed systemic hypotension. In addition, pulmonary vascular resistance and heart rate decreased. Dopamine infused under similar circumstances induced a similar increase in cardiac output and mean arterial pressure. Unfortunately, pulmonary artery pressure rose by approximately 30% and tachycardia developed in some of the patients. Dopamine was recommended over dobutamine when cerebral and coronary perfusion pressures required support.[4, 37]

Another inotropic agent that should be considered following acute pulmonary embolism is norepinephrine. This is suggested by Dehring and Arens,[13] who described the case of a 65-year-old man with pulmonary embolism. Norepinephrine infusion in this acutely ill individual produced increased cardiac output and systolic arterial pressure with corresponding decreases in CVP and pulmonary capillary wedge pressure (PCWP) after volume infusion and dopamine administration were ineffective.[13, 61] Animal work supports the utility of norepinephrine for increasing coronary perfusion in experimental acute right ventricular failure. The result of this therapy was improvement in cardiac output and decreased right ventricular end-diastolic pressure (RVEDP) in dogs with severe right ventricular failure due to blood clot embolization. In another canine study, phenylephrine infusion also reversed right ventricular ischemia, decreased RVEDP, and increased blood pressure, cardiac output, and right coronary blood flow when severe right ventricular failure was induced along with systemic hypotension due to autologous clot infusion.[63, 74, 80]

There have been no clinical studies examining the use of hydralazine in acute pulmonary thromboembolism. However, oral administration of this agent to patients with chronic pulmonary hypertension caused either an increase in cardiac output with decreased pulmonary arterial pressure or systemic hypotension with associated symptoms. A case report does suggest that hydralazine may be of use in acute pulmonary thromboembolism after failure of dopamine to support the circulation.[2] Hydralazine and nitroprusside have been compared in dogs with cardiac output diminution secondary to autologous clot infusion. Hydralazine returned cardiac output to baseline after a 40% to 50% decrement, whereas nitroprusside produced systemic hypotension without improvement in cardiac output or reduction in pulmonary vascular resistance. This response to hydralazine was thought to result from decreased mean pulmonary vascular outflow without change in pulmonary vascular resistance. Nitroprusside was detrimental in this situation owing to a reduction in right ventricular perfusion.[43]

The use of inotropes and pulmonary vasodilators such as norepinephrine and the prostaglandins is theoretically attractive. Unfortunately, no selective pulmonary vasodilators are now available and systemic vascular dilation may be detrimental in patients with severe acute pulmonary thromboembolism.[13]

Finally, the impact of acute administration of tissue plasminogen activator (TPA) on right ventricular dysfunction in patients with pulmonary thromboembolism was studied in a small number of individuals using serial Doppler echocardiographic studies. Right ventricular chamber enlargement was reversed, and right ventricular wall movement, which was mildly to severely compromised in some patients, normalized or improved in all individuals. Tricuspid regurgitation with right ventricular failure was also improved after this therapy. These investigators suggest that this early reversal of right ventricular dysfunction warrants consideration of TPA in patients with pulmonary embolism who present with serious hemodynamic compromise.[10]

THE PULMONARY VASCULAR BED

Anatomy/Physiology

As noted by Prewitt, right ventricular afterload increases with an alteration in the pulmonary vascular bed; however, despite the importance of these changes, the pathophysiology of acute pulmonary hypertension has only recently been elucidated.[63] Conventional pulmonary vascular resistance, calculated as pulmonary artery pressure minus left ventricular filling pressure divided by cardiac output, is assumed to reflect the flow resistance of the pulmonary vascular bed. Changes in pulmonary vascular resistance are thought to reflect changes in effective vascular caliber. A single pressure-flow coordinate is employed to describe the vascular resistance; the assumption is made that the effective pulmonary vascular outflow pressure in West zone III is equal to the left ventricular filling pressure.[81]

Recent work by several authors, using multicoordinate pulmonary vascular flow plots to investigate physiology and pathophysiology, has evaluated the pulmonary circulation.[15, 30, 31, 54, 55, 81] A linear relationship has been reported to exist between incremental resistance and flow in the pulmonary vascular bed. This incremental resistance, however, must be distinguished from traditional pulmonary vascular resistance, as the extrapolated pressure intercept in these studies may exceed left ventricular filling pressure in West zone III and alveolar pressure in West zone II. Thus, in the presence of pulmonary hypertension, the actual level of pulmonary artery pressure may result from an increase in the extrapolated pressure intercept, an increase in vascular resistance, or a combination of these factors. Vasoactive compounds may alter pulmonary hemodynamics by their effects on these factors together or individually.

To express this relationship graphically, a plot of upstream pressure (mean pulmonary artery pressure) against cardiac output, assuming a linear correspondence, should yield a straight line with the extrapolated pressure axis intercept reflecting the relevant downstream pressure. In isolated lobe experiments, this pressure-flow relationship has been described using determinations of pressure-flow coordinates at several levels of cardiac output.[30, 31] These studies reveal that the extrapolated pressure intercept of the linear segment exceeded the apparent downstream pressure. These investigators suggest that extrapolated pressure intercepts obtained from this animal work represent the mean closing pressure of the pulmonary vasculature and thus optimally represent the operative downstream pressure. The slope of the linear segment of the pressure flow plots obtained represents the incremental pulmonary vascular resistance. It is this derived closing pressure and the incremental resistance rather than the classic pulmonary vascular resistance that may vary in the setting of pulmonary hypertension, such as that following pulmonary thromboembolism. While pulmonary vascular resistance, as traditionally calculated, may change with a given intervention, incremental vascular resistance, as defined by the pressure-flow relationships described above, may not be affected. Data obtained from numerous animal experiments reveal that the incorrect assumption in the classic evaluation of pulmonary vascular resistance is that the appropriate downstream pressure in this relationship is the left ventricular end-diastolic pressure.[16]

Impact of Pulmonary Embolism

The initial hemodynamic result of pulmonary embolism is acute reduction in the area of the pulmonary vascular bed.[6, 58] While subsequent hemodynamic consequences may be secondary to this, other mechanisms may also play a role. With acute reduction in the patent pulmonary vascular bed, pulmonary artery pressure (PAP) increases and right ventricular work must also increase to compensate. Normal pulmonary vascular reserve is such that 50% of the cross-sectional area must be lost before sustained pulmonary hypertension will be seen at normal levels of cardiac output. With more than 50% of the pulmonary vascular bed occluded, pulmonary hypertension may result. Under these circumstances, the pulmonary artery pressure rises in direct relation to the degree of occlusion.

McIntyre and Sasahara[52] evaluated angiographic and hemodynamic findings in patients with pulmonary thromboembolism who had no preexisting cardiopulmonary disease. The correlation obtained by these investigators between mean PAP and pulmonary vascular obstruction suggested that a PAP of 22 mm Hg corresponded to a 30% obstruction of the pulmonary vascular bed, whereas a mean pulmonary artery pressure of 36 mm Hg corresponded with a 50% occlusion of the pulmonary vascular bed.[13, 52] There was no correlation between angiographic findings, cardiac output, or pulmonary artery pressure in patients with chronic cardiopulmonary disease. In some patients with small pulmonary thromboemboli, the cardiac index was severely depressed. The combination of pulmonary capillary wedge pressure and PAP was not a reliable indicator of the magnitude of pulmonary embolism in patients with preexisting congestive cardiac failure and superimposed pulmonary thromboembolism.[51]

In addition to the direct effect of vascular occlusion by thromboemboli as a cause of pulmonary hypertension, there is indirect evidence supporting mediator-induced vasoconstriction.[13] For instance, as noted above, mean PAP increased to an average of 35 mm Hg when 50% of the pulmonary vascular bed was occluded by emboli, whereas this value increased from an average of 17 to only 23 mm Hg with unilateral pulmonary occlusion in healthy volunteers.[83] Microemboli induced more mediator release, pulmonary permeability changes, and reflex effects than did larger obstructing emboli in a variety of animal studies.[8, 38, 49] The clinical relevance of this animal work must be viewed with some skepticism, as pulmonary hypertension created by microemboli may be more amenable to vasodilation and manipulation of mediators than larger, more clinically significant, pulmonary emboli. In addition, anesthetics and other drugs given in animal studies may affect the response of the sympathetic nervous system and thus provide misleading information.[13]

In light of the above findings, vasoactive mediator blockade has theoretical appeal and is supported by a variety of animal studies.[13] Treatment with aspirin, a prostaglandin synthesis inhibitor, decreased mortality from 55% to 0% in rabbits embolized with autologous clot. A similar result was obtained with methysergide, a serotonin antagonist, using a similar protocol.[79] Improved hemodynamics and oxygen transport were noted along with reduction in extravascular lung water when kentaserin was administered after infusion of autologous clot in a canine study.[36, 78] Unfortunately, the benefit from kentaserin was less significant in 10 heparinized patients treated with this agent in the presence of non–life-threatening pulmonary thromboembolism. Changes in arterial partial pressure of oxygen tended to be small as were the alterations in pulmonary artery and mean arterial pressures. Cardiac index was unchanged.[13, 35]

Other reports suggest that sympathetic blockade is beneficial if performed within hours of the onset of acute symptoms from pulmonary thromboembolism. Stellate ganglion block has been noted to reverse pulmonary artery vasospasm and decrease pressure gradients of as high as 25 mm Hg across the right ventricular outflow tract. The benefit of this therapy in the presence of heparin administration is unclear. Some of these data originate in case reports from the 1940s and 1950s, where nonheparinized patients with pulmonary thromboembolism experienced relief of chest pain, cyanosis, dyspnea, and shock.[13, 19, 20]

HEMODYNAMIC MANAGEMENT OF PULMONARY THROMBOEMBOLISM

Management Principles

In a canine study, Duval and associates[18] investigated the effects of pulmonary thromboembolism and norepinephrine on the previously described pulmonary pressure flow characteristics.[16] Multiple parameters, including PAP and cardiac output, were obtained by opening systemic arterial-venous fistulae fitted with variable resistors. Embolization in this study produced significant pulmonary hypertension, with a threefold increase in pulmonary artery pressure and a fourfold increase in calculated pulmonary vascular resistance. When the pulmonary vascular pressure-flow data were plotted, however, these authors[15, 17] noted only a small increase in the overall mean incremental resistance (slope of the curve relating PAP to cardiac output). The increase in incremental resistance was much less than that suggested by the traditionally calculated pulmonary vascular resistance. Instead, there was a marked upward shift in the extrapolated pressure intercept, suggesting that the predominant mechanism of the increase in pulmonary artery pressure in this model was an elevation of the mean pulmonary vascular closing pressure, not a change in vascular resistance.

In a second arm of this study,[17] norepinephrine was administered and the pulmonary artery pressure and cardiac output measurements were repeated. Before and after embolization, norepinephrine caused a significant increase in cardiac output and decreased the traditionally calculated pulmonary vascular resistance. When pulmonary vascular pressure-flow curves were calculated, however, norepinephrine did not in fact alter the slope of the curve (incremental resistance) (Fig. 5). Thus, the utility of norepinephrine therapy in pulmonary thromboembolism rests on reversal of the shock state by its beneficial pressor effects, whereas its inotropic effects improve right ventricular function.

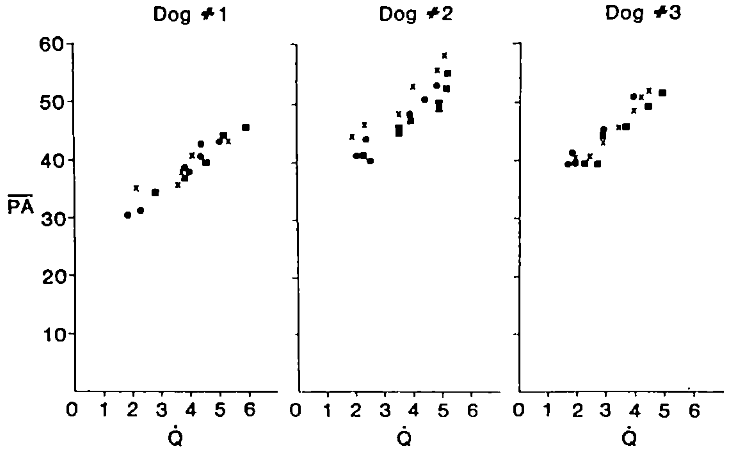

Figure 5. The PA-CO coordinates for three dogs after embolization are plotted prior to norepinephrine (NE) (x), during NE (■), and time control after NE infusion (●). For each dog, analysis of covariance revealed no differences in slope. Q = cardiac output, 1/min. (*From* Ducas J, Prewitt RM: Pathophysiology and therapy of right ventricular dysfunction due to pulmonary embolism. *In* Brest AN, Fisk RL (eds): Cardiovascular Clinics: The Right Heart. Philadelphia, FA Davis, 1987, pp 191–202; with permission.)

These positive changes are not associated with any pulmonary vascular effects. Any increase in pulmonary artery pressure with norepinephrine therapy is thought to be due to the change in right ventricular outflow.[16] Ducas and Prewitt cite clinical studies that also fail to demonstrate an increase in pulmonary vascular tone with norepinephrine administration.[25, 28]

Hydralazine has also been noted to have a beneficial hemodynamic impact in clinical and canine studies of pulmonary hypertension. Increased cardiac output without a change in pulmonary artery pressure suggests that hydralazine has a specific pulmonary vasoactive property.[16] These effects were studied by Ducas and Prewitt in a canine model of autologous clot embolization similar to that described previously.[15, 18] Pulmonary vascular pressure-flow relationships were determined before and after pulmonary embolization and hydralazine therapy. Hydralizine doubled cardiac output, whereas calculated pulmonary vascular resistance decreased. Pulmonary artery pressure was unaffected. The pulmonary artery pressure–cardiac output characteristics of the pulmonary circulation were plotted. While an increase in incremental resistance was noted with embolization, the major explanation for the increase in pulmonary artery pressure was a large change in the closing pressure, as described above (Fig. 6). The effect of

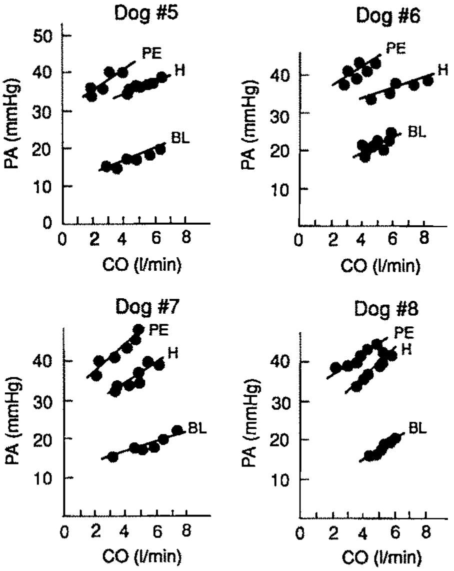

Figure 6. The PA-CO coordinates for four dogs are plotted at baseline (BL) prior to embolization, after embolization with autologous blood clots (PE), and following administration of hydralazine (H). The differing levels of CO in each condition were produced by opening arteriovenous fistulae. (*From* Ducas J, Prewitt RM: Pathophysiology and therapy of right ventricular dysfunction due to pulmonary embolism. *In* Brest AN, Fisk RL (eds): Cardiovascular Clinics: The Right Heart. Philadelphia, FA Davis, 1987, pp 191–202; with permission.)

hydralazine was not to reduce pulmonary vascular resistance but to induce a parallel downward shift in the pressure-flow curves, again consistent with a decrease in the pulmonary vascular closing pressure rather than reduction in incremental vascular resistance.[16]

Thus, an increase in vascular closing pressure rather than a change in incremental resistance is the principal mechanism explaining the increase in right ventricular afterload following pulmonary thromboembolism. Treatment intended to reduce right ventricular afterload may act by a reduction in closing pressure and in incremental resistance. These factors must be weighed along with other therapeutic considerations in hemodynamic manipulation designed to augment right ventricular performance after pulmonary thromboembolism.

Summary of Therapeutic Concepts

In patients with pulmonary thromboembolism who have a marked diminution in cardiac output and blood pressure complicating an increase in right ventricular afterload, initial therapy should ensure appropriate right coronary perfusion pressure.[63] Norepinephrine, a drug with inotropic and pressor effects, is an excellent agent for short-term maintenance of hemodynamic stability. If a moderate decrease in cardiac output complicates the increased afterload, dobutamine, or possibly isoproterenol, may be used to increase right ventricular output. However, these agents may decrease systemic vascular resistance and systemic blood pressure; thus, right ventricular coronary perfusion pressure as inferred from arterial pressure, pulmonary artery pressure, and central venous pressure must be carefully monitored. In these critically ill patients, endpoints of therapy should be guided by invasive hemodynamic monitoring.[63]

In the canine studies reviewed previously in this article, data suggest that changes in incremental resistance and effective outflow pressure are responsible for the increase in pulmonary artery pressure seen with thromboembolism.[63] Thus, vasoactive drugs may improve hemodynamics in the pulmonary vascular bed and decrease right ventricular afterload by reduction in either or both of these parameters. Norepinephrine and hydralazine may be effective for this purpose. Finally, a recent hemodynamic study using a canine model of pulmonary embolism investigated the improvement in pulmonary hemodynamics with the administration of TPA as thrombolytic therapy. Pulmonary pressure-flow relationships were studied before and after infusion of TPA by varying the cardiac output with systemic fistula creation. As noted previously, emboli increased pulmonary artery pressure from 15 to 37 mm Hg, with the change predominately due to an increase in the effective outflow pressure. Acute administration of TPA eliminated this pressure increase within an hour after onset of treatment.[66]

As the majority of deaths complicating pulmonary thromboembolism occur soon after the onset of symptoms, a thrombolytic regimen that induces rapid thrombolysis is indicated. Recent data suggest that acute administration of TPA may be the therapy of choice in the setting of circulatory instability complicating pulmonary thromboembolism.[27, 29, 70, 73]

Anesthetic Implications of Pulmonary Embolism with Hypertension

There is little discussion of the patient with severe ventricular dysfunction secondary to pulmonary embolization in the anesthetic literature. The general approach to the management of this patient group is the same as that for any with severe ventricular dysfunction, namely, high-dose opioid administration.[1, 5] The role of supplemental anesthetic agents is controversial in this setting. In a recent study, investigators at Loyola University Medical Center and Mount Sinai Medical Center[40] used rapid-response thermistor pulmonary arterial catheters and transesophageal echocardiography to examine the effects of nitrous oxide on ventricular function and the pulmonary circulation during high-dose fentanyl anesthesia. Ten individuals with pulmonary hypertension receiving elective mitral valve repair or replacement were studied. Pulmonary hypertension was defined as a mean pulmonary artery pressure greater than 35 mm Hg at cardiac catheterization. Coexisting coronary artery disease was grounds for exclusion. All patients ranged from 40 to 70 years of age and were American Society of Anesthesiology class 3 or 4. Hemodynamic measurements included heart rate, mean systemic arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, and right atrial pressure. Pulmonary vascular resistance and right ventricular stroke work were calculated using standard formulae. Thermodilution data were collected using a rapid-response thermistor catheter and cardiac output computer. The anesthetic technique employed intravenous fentanyl and pancuronium with supplemental nitrous oxide as the inhaled agent. Echocardiographic data were analyzed by tracing end-systolic and end-diastolic areas from four consecutive cardiac cycles using an electric pen and an activated grid system calibrated for each recording.

Nitrous oxide was associated with a statistically significant decrease in mean arterial pressure, mean pulmonary artery pressure, and cardiac output. Administration of 100% oxygen after nitrous oxide administration resulted in an additional decline in heart rate, mean arterial pressure, mean pulmonary artery pressure, and cardiac output. There was no change in right ventricular performance as assessed by echocardiography, and while the changes in hemodynamic variables were statistically significant, they were not felt to be clinically meaningful.

These workers concluded that nitrous oxide is an appropriate supplemental anesthetic agent in combination with a high-dose narcotic technique to lessen intraoperative awareness and blunt the hemodynamic response to surgical stimulation. Nitrous oxide is attractive in

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this role owing to its rapid onset of action and rapid elimination in the event of deleterious consequences. It is also an effective analgesic and amnestic capable of suppressing the response to surgical stimuli in pediatric patients and in providing sedation and control of blood pressure in adults during thoracic surgical procedures.[1, 40]

The use of nitrous oxide in the presence of pulmonary hypertension has been restricted by concern about the potential for an increase in pulmonary vascular resistance and right ventricular dysfunction. In studies of nitrous oxide in combination with morphine, Wong and colleagues[85] and Lappas and colleagues[41] suggest that pulmonary vascular resistance and mean pulmonary artery pressure may increase. Schulte-Sasse and associates[69] noted increased pulmonary vascular resistance and mean pulmonary artery pressure in patients given nitrous oxide in combination with halothane, fentanyl, or diazepam. Unfortunately, the anesthetic techniques employed in these studies were somewhat different in each case. In addition, we must recognize that these data are extrapolated from pulmonary hypertension as a result of cardiac disease to the setting of embolization. Clearly, in terms of mediator release and hemodynamic properties, these two situations, though similar, are not identical. In addition, as previously noted, the right ventricle is highly compliant, so that large volume changes may occur before measurable changes in right atrial or other pressures occur. Finally, right ventricular afterload varies with time and cardiac cycle, and is poorly represented by pulmonary vascular resistance. Thus, on the basis of limited clinical data and a limited number of hemodynamic measurements, a high-dose narcotic technique with cautious supplementation utilizing nitrous oxide, as permitted by systemic oxygenation, are recommended for the anesthetic management of patients facing acute cardiopulmonary compromise secondary to pulmonary thromboembolism.

SUMMARY

The hemodynamic consequences of acute obstruction of the pulmonary arterial tree result from physiologic changes in the pulmonary circulation. Normal mean pulmonary arterial pressure, about 12 to 15 mm Hg, is one-sixth to one-eighth the systemic pressure. Acute reduction in pulmonary vascular cross-sectional area creates a sudden increase in output load on the right heart chambers resulting in right heart failure. In the absence of preexisting cardiovascular disease, right ventricular decompensation sets in at a mean pressure in the pulmonary artery of approximately 40 mm Hg. At this point, performance of the thin-walled right ventricle deteriorates dramatically. Support of the pulmonary circulation begins with volume resuscitation and inotropic support for the right ventricle. Right coronary perfusion should also be optimized through support of aortic root pressure. Afterload stress to the right ventricle may be reduced with oxygen therapy. There are no other reliable selective pulmonary vasodilators available at this time.

The impact of pulmonary embolization and therapy supportive of right ventricular function have recently been studied through assessment of incremental resistance in pulmonary vascular pressure flow curves. The utility of agents such as norepinephrine was confirmed in this model that revealed improved right ventricular function without deterioration in pulmonary vascular bed response. More recent studies utilizing thrombolytic therapy also suggest improved response of the right ventricle and pulmonary vascular bed with immediate administration following pulmonary embolic events. Finally, there are few data describing the utility of different anesthetic regimens in the management of patients during acute cardiopulmonary compromise secondary to pulmonary thromboembolism. Based on the limited data available, a narcotic technique with supplementation using nitrous oxide in inspired concentrations that allows adequate oxygenation can be recommended.

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EFFECTS OF PULMONARY EMBOLISM ON THE LUNG

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The lung acts as a filter of the blood, entrapping a wide variety of particulate matter. It is likely that trapping of small amounts of cellular debris or thrombin clots in the pulmonary capillary bed is not unusual in normal individuals. No known physiologic effects have been ascribed to this "routine microembolization." However, under certain circumstances, the lung may encounter a significant embolic burden that causes marked alterations in pulmonary function.

Much of the information about the effects of embolization on lung function is based on experimental studies in animals. These have often led to disparate conclusions, depending on the composition of the material embolized, the size of the particles, and the animal species studied. The response to pulmonary embolism in humans also varies depending on the type of material embolized (Table 1). Thromboemboli, the most important clinical embolic problem, originate predominantly in the large veins of the iliofemoral system and thus occlude large pulmonary arteries. The pathophysiologic response to thromboemboli is complex, involving both direct and reflex effects of vascular occlusion as well as the release of various vaso- and bronchoactive mediators.

The reaction to other embolic material, including fat, bone marrow, amniotic fluid, and air in the clinical and experimental setting, as well as to glass beads and thrombin in the experimental laboratory, is more consistent with an acute lung injury and the clinical picture of noncardiogenic pulmonary edema.[19, 31] All of these insults are microembolic in nature and the mechanism of injury is thought to be neutrophil-

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induced damage to the pulmonary microvessels rather than vascular occlusion.[1, 20]

Septic embolism, once a rare event seen in association with septic pelvic thrombophlebitis, has become more common because of the explosion in intravenous drug abuse. The major consequence of septic embolization is pulmonary infection, presenting with scattered pulmonary infiltrates on chest radiographs and a clinical picture of pneumonia.[25] An additional complication of intravenous drug abuse is embolization of the lung with particles and "fillers" such as talc. In addition to the effects of chronic occlusion of the pulmonary vascular bed, these particles often set up a local inflammatory response that may eventually result in the development of respiratory insufficiency with both obstructive and restrictive features.[38]

Thromboembolism is far and away the most common clinical pulmonary embolic phenomenon, and the remainder of this article is devoted to it. Whenever possible, the discussion is based on human data. However, in the case of acute embolization, patients are often too sick to study in detail and thus much of what we understand is based on animal studies. Direct extrapolation of these data to humans should be made with caution. In the case of chronic embolic disease, a good animal model does not exist and thus the data are necessarily limited.

ACUTE THROMBOEMBOLIZATION

Effects on Pulmonary Mechanics

The effects of acute thromboembolism on lung mechanics in humans are unclear, since, as we have noted above, there have been no adequate studies. In animals, the earliest response to embolization is an increase in airway resistance, a fall in frequency-dependent dynamic compliance, and a fall in static compliance.[5, 43, 45] These changes occur immediately following impaction of the emboli, are maximal at 2 minutes, and last for about 30 to 40 minutes. They are accompanied by a reduction in lung volume and are reversed by isoproterenol administration, suggesting that these alterations in the dynamic and static properties of the lung are at least in part due to bronchoconstriction.

Table 1. TYPES OF PULMONARY EMBOLI

Material	Consequence
Thrombi	Vascular obstruction
Air, fat, amniotic fluid	Vascular damage and pulmonary edema
Septic	Pneumonia
Foreign body	Vasculitis and fibrosis

In some studies,[43] the changes in airway resistance could be blocked by vagotomy.

Anatomic studies in dogs and cats have demonstrated that the physiologic alterations in lung mechanics are accompanied by constriction of the alveolar ducts and small airways but not of the larger airways.[8] This suggests that the decrease in lung volume and in static and dynamic compliance are due to small airway constriction. The increase in airway resistance, a variable finding in different studies, which indicates some participation by larger airways in the response to embolization, has also been ascribed to the decrease in lung volume with a possible additional contribution from increased vagal tone.[43] Because these changes are localized to lung segments distal to the embolized vessels and are blocked by pretreatment with heparin and blockers of serotonin, they are thought to be due to the release of vasoactive amines from platelet aggregates within the thrombus.

Pulmonary edema is not as prominent following occlusion of major vessels as it is subsequent to microembolization, although it has been reported after experimental large-vessel occlusion.[4, 26] To the degree to which it occurs, pulmonary edema may also play a role in the observed changes in lung mechanics. These effects, however, are relatively mild. Interstitial water accumulation has a minimal effect on the pressure-volume curve of the lung and even alveolar flooding decreases lung compliance by only 20% to 30%.[23, 35, 42] The effect of interstitial edema on airway resistance is somewhat more significant when the edema is secondary to increased postcapillary pressure; this is thought to result mainly from compression of the small peripheral airways by engorged vessels as they compete for space within the lung interstitium.[24] Whether or not interstitial fluid accumulation alone, as might be seen in the setting of pulmonary embolism, is capable of similarly compressing the airways is unclear.

A decrease in surface-active material distal to the occluded vessels is thought to be the cause of the hemorrhagic atelectasis seen after acute pulmonary thromboembolization.[7] Because the reduction in surfactant occurs 18 to 24 hours after the acute event, however, it is unlikely to explain any of the acute changes described in the animal studies.

No measurements of pulmonary compliance or airway resistance have been made in humans during the acute event. Decreases in lung volume are, however, suggested by the acute findings on chest radiographs (atelectasis, elevated diaphragm).[46] Wheezing has been also described following acute thromboembolization, although it is unlikely that constriction of small airways (1–3 mm) could give rise to this symptom.

Dyspnea and rapid shallow breathing are among the most common findings in patients with acute pulmonary thromboembolism. This has suggested that emboli may stimulate the pulmonary chemoreflex by activating the pulmonary C fibers (J receptors).[18] In animals, this reflex induces bradycardia, hypotension, and apnea followed by rapid shallow breathing. Experimentally, stimulation of C fibers has been observed following embolization by starch and plastic beads.[2] C fibers can also be stimulated in some animal species by prostaglandins (PGI_2 and PGE_2) as well as serotonin.[3, 9, 37, 41] These substances have been reported to be released in experimental acute pulmonary embolization. Irritant receptors may also be activated by experimental embolization.[33] They initiate tachypnea, hyperventilation, and reflex bronchoconstriction. However, once again, there are no human data for any of these responses. Thus, while it is clear that pulmonary emboli alter the breathing pattern, the mechanism remains to be elucidated.

Effects on Pulmonary Gas Exchange

Abnormal pulmonary gas exchange is an almost inevitable consequence of acute pulmonary thromboembolism. Of the patients entered into the Urokinase Pulmonary Embolism Trial, only 11.5% had an arterial oxygen tension (Pa_{O_2}) greater than 80 mm Hg.[46] In another series of patients with proven pulmonary embolism, 13% had a Pa_{O_2} greater than 80 mm Hg and in only 6% was it greater than 90 mm Hg.[13] Thirty-two percent of these patients had severe hypoxemia with a Pa_{O_2} of less than 60 mm Hg (Fig. 1). In two studies, only 5% of the patients had a normal alveolar-arterial O_2 gradient ($A\text{-}aDO_2$).[10, 36] In patients without preexisting lung or heart disease, there is a good correlation between the degree of hypoxemia and the severity of the pulmonary vascular obstruction, but this is not the case in patients with prior cardiopulmonary disease.[30]

Hypocapnia is common, although perhaps not as universal as hypoxemia. In the previously mentioned clinical studies, 79% were hypocapnic ($Pa_{CO_2} < 37$ mm Hg) with 18% having a Pa_{CO_2} less than 26 mm Hg[13] (see Fig. 1). Hypocapnia or an abnormal $A\text{-}aDO_2$ was present in 98% of patients in one series of proven pulmonary emboli.[10] Even in patients with hypercapnic respiratory failure, acute pulmonary embolism has been associated with a reduction in the Pa_{CO_2}.[29] Because the degree of hypocapnia appears to be independent of the severity of the hypoxemia, it is unlikely that it is due to chemoreceptor stimulation. A more likely explanation relates to the aforementioned changes in breathing pattern.

The abnormal gas exchange in patients with acute pulmonary embolism results from a combination of mechanisms, including ventilation/perfusion ($\dot{V}A/\dot{Q}$) inequality, intrapulmonary and intracardiac shunting, diffusion impairment, and mixed venous hypoxemia. The importance of each of these factors varies from patient to patient.

In two series of patients with acute pulmonary emboli studied with the multiple gas elimination technique, increased $\dot{V}A/\dot{Q}$ inequality was a common finding.[22, 32] Both high and low $\dot{V}A/\dot{Q}$ units were found, although in individual patients either one or the other might predominate (Fig. 2). Shunt played a rather minor role, averaging only 5.4% in both studies and the ventilation of unperfused lung (dead space) was only mildly increased (mean of 45% and 52% of minute ventilation in

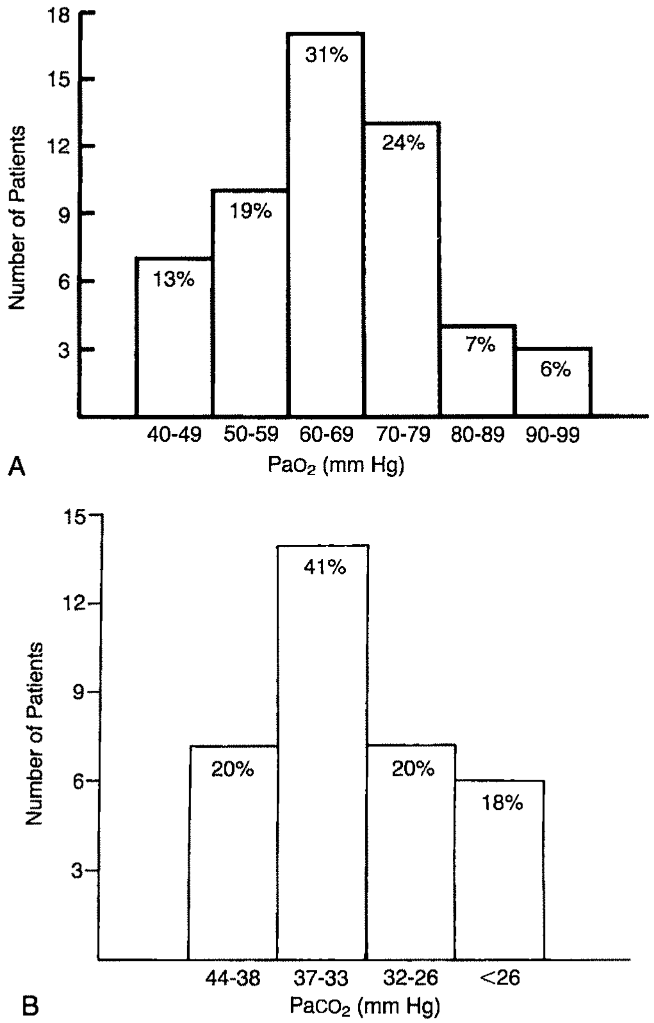

Figure 1. Arterial Po_2 *(A)* and Pco_2 *(B)* from 54 patients without previous cardiopulmonary disease and angiographically proven acute pulmonary embolism. (*Figure 1A from* Dantzker DR, Bower JS: Alterations in gas exchange following pulmonary thromboembolism. Chest 81:495–501, 1982; with permission.)

the two studies). In one of the reports, a small component of abnormal diffusion was demonstrated, which explained about 13% of the $A\text{-}aDO_2$.

The heterogeneity of the $\dot{V}A/\dot{Q}$ patterns seen in patients was predicted by animal studies of thromboembolism.[17] Following acute embolization with similar volumes of autologous clot in dogs, most animals developed broad bimodal patterns consisting of both low and high $\dot{V}A/\dot{Q}$ units. However, like the patients, some developed patterns in which the predominant change from the preembolization patterns

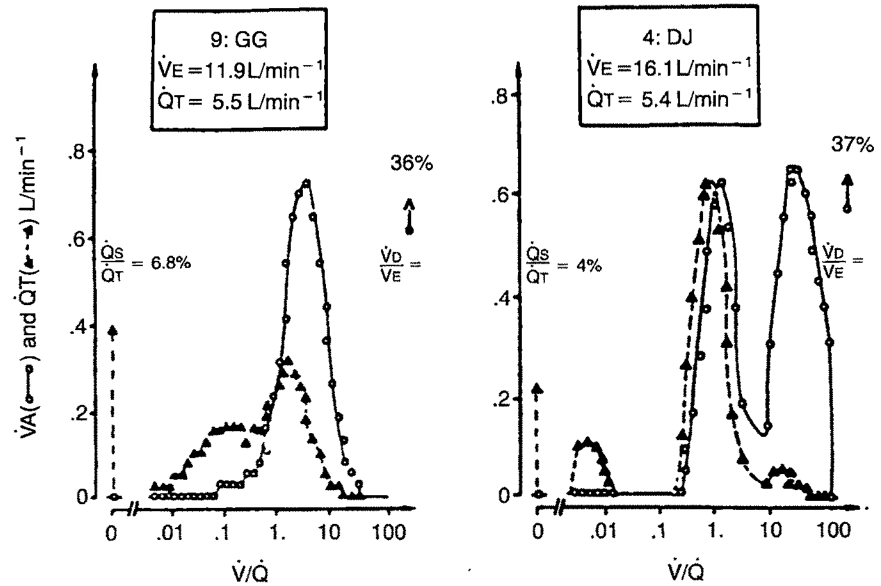

Figure 2. The distribution of ventilation ($\dot{V}_A$) and blood flow ($\dot{Q}_T$) plotted against the ventilation/perfusion ratio for two patients with acute pulmonary embolism. Two different patterns can be seen. Patient GG has a large amount of blood flow to low $\dot{V}A/\dot{Q}$, whereas the major abnormality in patient DJ is the presence of high $\dot{V}A/\dot{Q}$. Both patients have a small amount of shunt ($\dot{Q}_S/\dot{Q}_T$), but no increase in dead space ($\dot{V}_D/\dot{V}_E$). (*Modified from* Manier G, Castaing Y, Guenard H: Determinants of hypoxemia during the acute phase of pulmonary embolism in humans. Am Rev Respir Dis 132:332–338, 1985; with permission.)

was the development of either high or low $\dot{V}A/\dot{Q}$. In these animals, shunt was not increased and the increase in the ventilation of unperfused lung was small, averaging 6% immediately after embolization and falling to less than 3% at 30 minutes. Unlike the human studies, no evidence was found for impaired diffusion as a further cause of abnormal gas exchange.

The ability of a single insult to result in such a variability in $\dot{V}A/\dot{Q}$ patterns can be explained in part utilizing a simple two-compartment model (Fig. 3). Almost total occlusion of blood flow to a relatively small percent of the lung, as might result from a well-formed thromboembolus that stays intact after entering the pulmonary artery, results in high $\dot{V}A/\dot{Q}$ units in the embolized region. However, since a relatively small amount of blood flow is diverted to the remainder of the lung, low $\dot{V}A/\dot{Q}$ units are not created. Even in this setting, partial occlusion is probably more common than complete occlusion, as demonstrated by the minor or absent increases in dead space. If, on the other hand, the emboli involve a larger portion of the lung but impede a smaller fraction of the blood flow to the involved lung units, as might occur following fragmentation of the clot in the lung, then the $\dot{V}A/\dot{Q}$ of the embolized units will be less dramatically increased. However, the diversion of a relatively large volume of flow from a major proportion

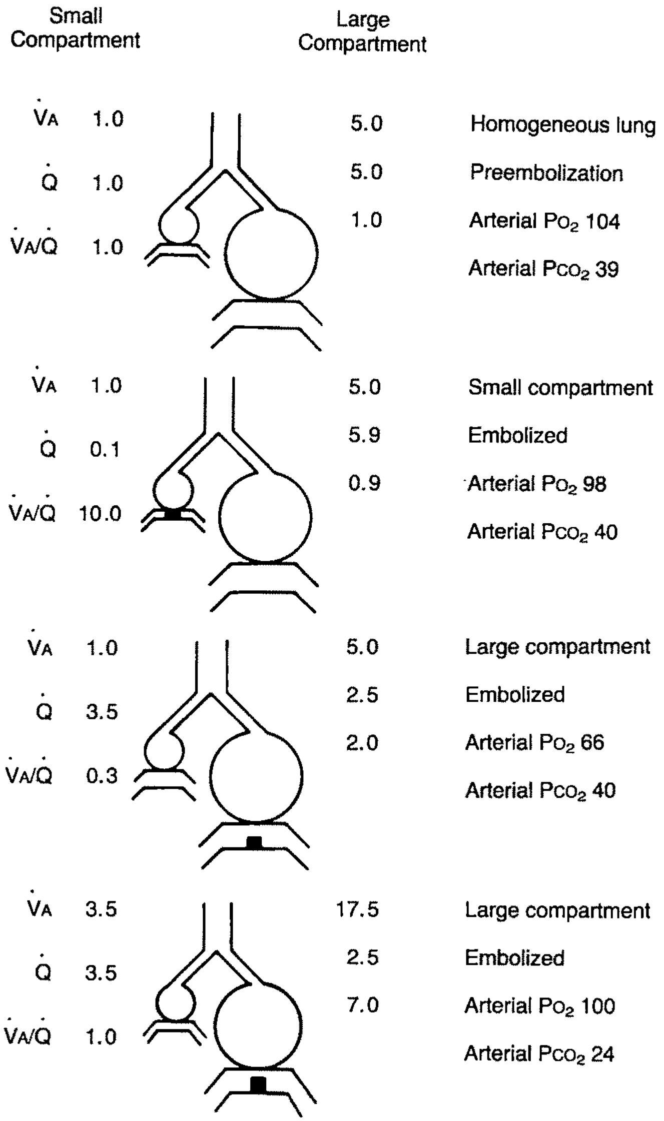

Figure 3. A two-compartment model used to explain the ventilation perfusion (V̇A/Q̇) inequality that occurs after pulmonary embolization. The lung has been divided into two unequal compartments, a small compartment and a large compartment, both with preembolization V̇A/Q̇ of 1.0. Embolization of the small compartment with almost total occlusion is demonstrated in the second panel. This results in the development of high V̇A/Q̇ units, but because only a small amount of blood flow is redistributed to the large compartment relative to its initial flow, there is very little change in the V̇A/Q̇ of the large compartment. Thus, no low V̇A/Q̇ units develop, and significant hypoxemia is absent. Embolization of the larger compartment by a clot that only partially occludes blood flow is shown on the third panel. Because only half the blood flow is occluded, the V̇A/Q̇ of the embolized compartment changes minimally, whereas more than 50% of the blood flow is now distributed to the small compartment, leading to the development of low V̇A/Q̇ units and resultant hypoxemia. To totally correct this situation, a large increase in ventilation would be required, as shown in the fourth panel, resulting in marked hypocapnia. (*From* Dantzker DR, Wagner PD, Tornabene VM, et al: Gas exchange after pulmonary thromboembolism in dogs. Circ Res 42:92–103, 1978; with permission.)

of the pulmonary vascular bed to the remaining unembolized region of the lung will create low $\dot{V}A/\dot{Q}$ units owing to overperfusion.

Conceivably, the $\dot{V}A/\dot{Q}$ in these areas could be normalized by an increase in ventilation to match the increase in perfusion. However, a completely compensatory ventilatory response would require a marked increase in minute ventilation and result in significant hypocapnia unless all of the additional ventilation could be directed only to the overperfused units, an unlikely scenario. While an attempt at compensation may be an additional component of the usually present low $Paco_2$ in these patients, it is likely that the marked hypocapnia that would be required for complete correction of the low $\dot{V}A/\dot{Q}$ units would blunt full compensation. A more even distribution of embolized and nonembolized lung would result in the more commonly observed pattern of both high and low $\dot{V}A/\dot{Q}$ units and permit partial ventilatory compensation in the overperfused lung units at more reasonable levels of minute ventilation.

In addition to this simple explanation for the observed $\dot{V}A/\dot{Q}$ inequality, it is also likely that the previously described changes in pulmonary mechanics and breathing pattern may also play a part, at least in the immediate postembolic period. In addition, reflexes that tend to constrain the development of $\dot{V}A/\dot{Q}$ inequality, such as hypoxic vasoconstriction and hypocapnic bronchoconstriction, may be operative. They could explain, in part, the rapid normalization of the $\dot{V}A/\dot{Q}$ distributions described in some animal studies as well as the relatively normal $\dot{V}A/\dot{Q}$ ratios seen in some patients.

While shunt was seen to play a relatively minor role in the previously described studies, it was a major factor in at least two patients with massive pulmonary embolism.[12] Since these patients had well-documented large-vessel occlusion and since there was no evidence for pulmonary edema, the shunt must be explained by other mechanisms. Shunting through newly opened pulmonary arterial-venous connections subsequent to an acute rise in right-sided pressures is a possibility. However, studies have failed to demonstrate, at least in experimental animals, the presence of intrapulmonary arterial-venous anastomoses despite fourfold elevations of pulmonary artery pressure.[6] The development of an intracardiac shunt would be a more likely right-to-left communication, especially since 15% of normal subjects have a probe-patent foramen ovale. The development of intracardiac shunting by this route has been demonstrated in some patients subsequent to massive acute pulmonary embolism.[21]

Postembolic atelectasis or infarction with continued perfusion around a partially obstructing clot or breakdown or partial dissolution of the initial thrombus with reperfusion of previously obstructed regions of the lung may provide an additional explanation for the acute development of shunt. The partial alleviation of hypoxemia during positive pressure ventilation or hyperventilation supports this mechanism.[48] Atelectasis following vascular occlusion may be due to a number of factors. Alveolar duct and small airway constriction as well as surfactant loss have already been discussed. In addition, bronchiolar constriction and pneumoconstriction have been demonstrated in the presence of regional hypocapnia in nonperfused or underperfused embolized lung regions.[34]

Factors other than direct alterations in lung function may also have a marked influence on arterial oxygenation. For any lung unit, the end capillary Po_2 is influenced by the mixed venous Po_2 (Pvo_2).[47] The magnitude of this effect depends on the $\dot{V}A/\dot{Q}$ of the unit. In the case of shunt, changes in Pvo_2 are directly translated into changes in the end capillary blood. For ventilated units the impact depends on the $\dot{V}A/\dot{Q}$; it is greatest for units with a $\dot{V}A/\dot{Q}$ of less than 1 and less if the $\dot{V}A/\dot{Q}$ is greater than 1. The manner in which this affects the Pao_2 depends on $\dot{V}A/\dot{Q}$ distribution as well as the degree of hyperventilation. Hyperventilation serves to shift the whole-lung $\dot{V}A/\dot{Q}$ ratio to a higher value, which depends on how evenly ventilation is distributed. In the presence of the $\dot{V}A/\dot{Q}$ inequality and shunt seen with acute pulmonary embolism, a low Pvo_2 can significantly amplify the resultant hypoxemia.

In one recent series of patients studied after acute embolization, it was calculated that only 1 of 10 patients studied would have had significant hypoxemia if their Pvo_2 had been normal.[32] Thus, the widened $A\text{-}aDO_2$ seen following pulmonary embolism probably overestimates the degree of vascular obstruction. Changes in the Pao_2 subsequent to the embolic event are as likely to represent alterations in cardiovascular function as they are to indicate changes in lung function.

CHRONIC THROMBOEMBOLIZATION

Lung Mechanics

Whereas there are no data on the changes in lung mechanics following acute pulmonary thromboembolism in humans, there are no animal studies of chronic unresolved pulmonary emboli. Since chronic pulmonary embolism is relatively uncommon, there also is not a large amount of clinical information. From the available data, it would seem that chronic occlusion of the pulmonary vessels has only a minor impact on lung mechanics and respiration. These changes are qualitatively similar to those found in other disorders characterized primarily by occlusion of large pulmonary vessels and thus may be more a consequence of the development of pulmonary hypertension than an effect of the emboli themselves. Specifically, there is an inconsistent and mild reduction of lung volumes in some patients and occasional mild airway obstruction.[28] The restrictive component is less obvious than that reported for patients with primary pulmonary hypertension with comparable degrees of pulmonary vascular obliteration.[40] Like patients with chronic pulmonary hypertension from other causes, hyperventilation and a chronic respiratory alkalosis are present both at rest and during exercise.[11] Since this is seen in patients with and without hypoxemia, it does not appear to be secondary to chemoreceptor stimulation. The cause of these mild abnormalities in lung mechanics and breathing pattern is unknown.

Gas Exchange

Patients with chronic unresolved pulmonary thromboemboli characteristically have moderate hypoxemia, which is exacerbated by exercise, and a chronic respiratory alkalosis. They have only mild to moderate $\dot{V}A/\dot{Q}$ inequality typified by a broadening of the major blood flow mode with some low and high $\dot{V}A/\dot{Q}$ units and a small amount of shunt[14, 28] (Fig. 4). In each patient, the concomitant finding of a low Pvo_2, predominantly due to low cardiac output, amplifies the effect of the $\dot{V}A/\dot{Q}$ inequality on arterial oxygenation much as in the acute phase. Finally, there is no contribution of diffusion impairment to the abnormal pulmonary gas exchange.

The etiology of the $\dot{V}A/\dot{Q}$ inequality in chronic embolic disease is unclear but it probably results from abnormalities of both blood flow and distribution of ventilation. The former is presumably the result of overperfusion of the open portion of the vascular bed and is likely to be the predominant abnormality. The ventilation abnormalities have been ascribed to interstitial pulmonary edema resulting from the high pulmonary artery pressures or from direct bronchial compression by dilation of adjacent pulmonary arteries.[24]

The rather mild degree of $\dot{V}A/\dot{Q}$ inequality and, in particular, the small amount of dead space relative to the apparent degree of vascular obstruction have been attributed to a number of factors. The inert gas technique tends to underestimate the dead space by as much as 20% when both series and parallel dead space are present.[39] In addition, it

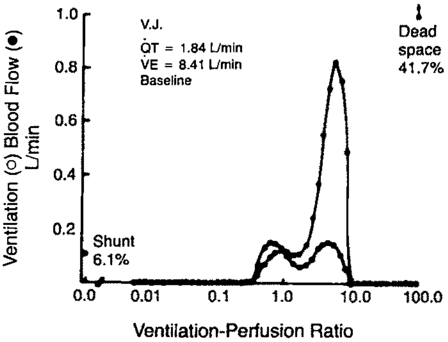

Figure 4. The ventilation (*open circles*) and blood flow (*closed circles*) distribution versus the ventilation perfusion ratio in a patient with chronic pulmonary embolic hypertension. Both high and low $\dot{V}A/\dot{Q}$ units are present, as well as a small degree of shunt. The dead space is only slightly elevated. (*From* Dantzker DR, Bower JS: Mechanisms of gas exchange abnormality in patients with chronic obliterative pulmonary vascular disease. J Clin Invest 59:203–216, 1979; with permission.)

has been suggested that a hypertrophied bronchial circulation, known to anastomose with precapillary pulmonary vessels in this setting, could provide sufficient perfusion to regions of obstructed pulmonary circulation to reduce the dead space.[27] There may also be compensatory mechanisms that tend to minimize the degree of $\dot{V}A/\dot{Q}$ inequality. The pulmonary hypertension of some patients with chronic embolic disease is partially reversible by vasodilators.[15] This reduction in vascular tone is invariably accompanied by increased $\dot{V}A/\dot{Q}$ inequality, suggesting that at least some of the associated pulmonary hypertension may result from an attempt to optimize pulmonary gas exchange.[16] Whether or not similar compensations are at work on the ventilation side is unknown. Hypocapnic bronchoconstriction has been demonstrated in humans after acute pulmonary artery occlusion but the duration of this response is unknown.[44]

SUMMARY

The pathophysiologic consequences of pulmonary thromboemboli on pulmonary function result both from the direct effects of vascular occlusion and from released vasoactive and bronchoactive mediators. All of these alterations in function are further modified by the effect of embolization on cardiac function, predominantly through modification of the Pvo_2. This complex interaction of events makes it difficult to clearly assign mechanisms to all of the observed changes in patients as well as to utilize changes in clinical values as a way of following the natural history of the vascular occlusion.

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INTERATRIAL SEPTUM AND ITS ROLE IN SYSTEMIC EMBOLISM

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and Frederick Feit, MD

The interatrial septum (IAS) is a complex structure, affected by respiratory, positional, and hemodynamic changes. While patent foramen ovale has long been among the differential diagnoses for systemic arterial embolism, there has been little insight into the events responsible for this phenomenon. With the development and refinement of cardiac imaging techniques over the past several years, an enormous body of knowledge has accumulated regarding the physiology and pathophysiology of the IAS. In fact, the septum is critically involved in systemic embolism through several mechanisms.

DEVELOPMENT

The two atria are formed from a single common chamber beginning at about 4 weeks of gestation (Fig. 1). The septum originates with the ingrowth of a tissue plane called the septum primum. As this grows inferiorly toward the endocardial cushions, which are to become an integral part of the tricuspid and mitral valve annuli, a small interatrial communication (the ostium primum) remains. The septum primum eventually fuses with the endocardial cushions, resulting in the closure of the ostium primum. However, during this growth, spontaneous perforations occur in the upper septum, which coalesce to form a second interatrial communication, the ostium secundum.

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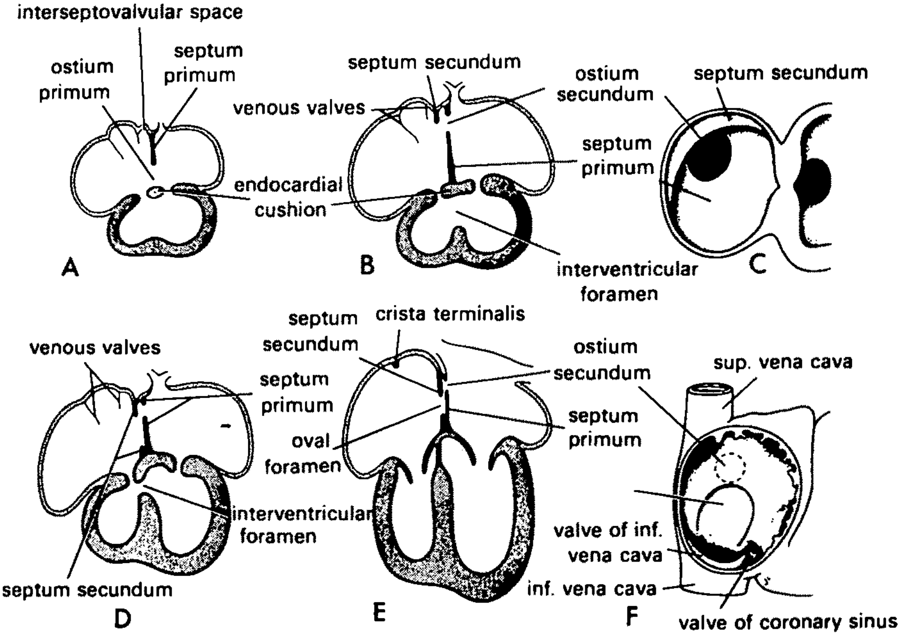

Figure 1. Schematic representation of the atrial septum at various stages of fetal development. *A*, At 6 mm (about 30 days). *B*, Nine millimeters (about 33 days). *C*, Same stage as in *B*, but seen from the right. *D*, Fourteen millimeters (about 37 days). *E*, Newborn. *F*, View of the atrial septum seen from the right, same stage as in *E*. (*From* Emmanouilides GC: *In* Moss AJ, Adams FH (eds): Heart Disease in Infants, Children and Adolescents. Baltimore, Williams and Wilkins, 1968; with permission.)

The septum secundum is a tissue plane formed by further growth and development of the two atria. It is a curtainlike structure extending down from the roof of the atria on the right side of the septum primum. The septum secundum overlaps the ostium secundum, thereby separating the right and left atria. However, a central opening remains in the septum secundum (the fossa ovalis), covered by a portion of the septum primum, which serves as the valve of the foramen ovale. Therefore, the integrity of the IAS is dependent on proper growth of the septum primum and septum secundum, as well as on proper fusion with the endocardial cushions.

The fetal circulation consists of pulmonary and systemic circuits arranged as parallel pathways, in contrast to the postpartum state in which these circuits are arranged in series. In the fetus, the lungs are collapsed and not functional. The resistance of what is only a potential pulmonary vascular circuit is therefore quite high, and blood is shunted away from it in two major ways (Fig. 2). Oxygenated blood returns from the placenta via the umbilical vein and enters the portal venous system. This flow then largely bypasses the hepatic circulation, entering the inferior vena cava via the ductus venosus. There it combines with the hepatic and lower body venous returns and enters the right atrium.

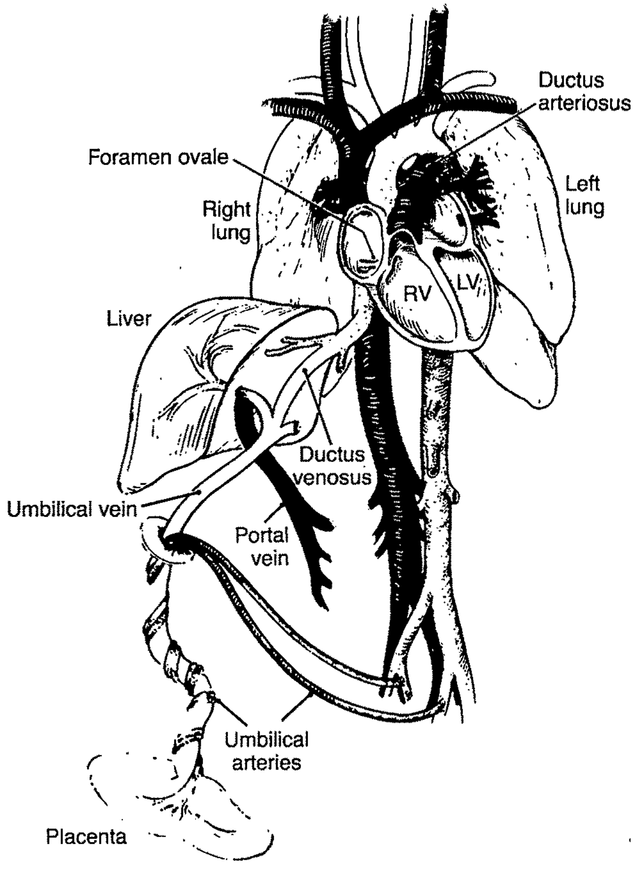

Figure 2. Human fetal circulation. Intensity of dots within vessels indicates degree of oxygen desaturation of hemoglobin. Note possible course of blood from the placenta through the liver or through the ductus venosus to the inferior vena cava, and then to the heart. Note major sites of mixing of blood streams of varying oxygen content: portal vein, hepatic vein, inferior vena cava, foramen ovale, and ductus arteriosus. (*From* Emmanouilides GC: *In* Moss AJ, Adams FH (eds): Heart Disease in Infants, Children and Adolescents. Baltimore, Williams and Wilkins, 1968; with permission.)

With the help of a curtainlike structure called the eustachian valve, located at the junction of the inferior vena cava and right atrium, about 70% of this right atrial inflow is directed across the foramen ovale into the left atrium and thus returns to the systemic circulation. The remaining 30% enters the right ventricle along with most of the effluent from the superior vena cava and the coronary sinus. Flow from the right ventricle to the pulmonary artery mainly enters the aorta via the ductus arteriosus. Only a small amount of blood actually traverses the pulmonary circuit.

It is clear that fetal hemodynamics and cardiac development are closely related. For instance, flow via the foramen ovale is critical for development of the left ventricle, as premature closure of the foramen ovale results in left ventricular hypoplasia.[26]

With inflation of the lungs at birth there is a marked decrease in pulmonary vascular resistance, leading to a pronounced increase in the pulmonary circulation and a resultant rise in pulmonary venous blood flow into the left atrium. Loss of the low-resistance placental circuit leads to an elevation in the systemic vascular resistance that in combination with the increased left atrial inflow produces a rise in left atrial pressure. This pressure increase pushes the septum secundum and the septum primum together, closing the foramen ovale. These structures usually fuse over time.

In about 50% of persons up to 5 years of age and 25% of persons older than 20 years of age, fusion of the septa is incomplete and a small potential communication persists. This situation is termed "probe-patency" of the foramen ovale. The presence of a probe-patent foramen ovale, which we will refer to simply as patent foramen ovale (PFO), does not necessarily result in blood flow between the atria.[26, 80, 93]

NORMAL AND PATHOLOGIC ANATOMY

The Normal Interatrial Septum

After infancy, the interatrial septum is a membrane that is usually thicker at its periphery than at its center, with the fossa ovalis being the thinnest portion (Fig. 3). In a group of adults undergoing transesophageal echocardiography (TEE), the average diastolic thickness of

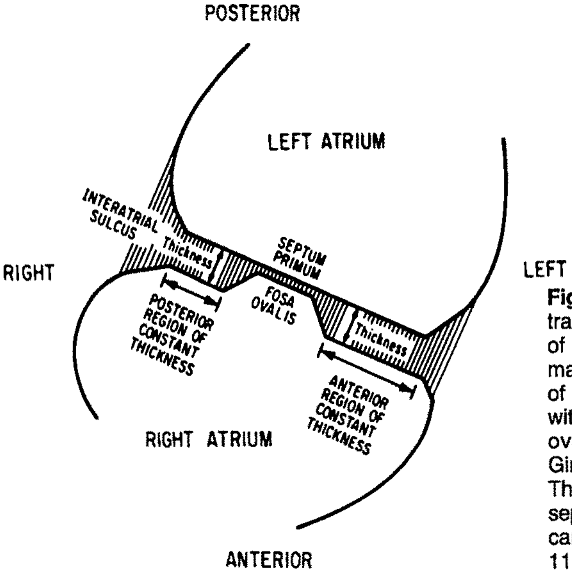

Figure 3. Schematic image of transesophageal echocardiogram of the interatrial septum. In the majority (82%) of patients, regions of constant thickness are noted, with abrupt thinning at the fossa ovalis. (*From* Schwinger ME, Gindea AJ, Freedberg RS, et al: The anatomy of the interarterial septum: A transesophageal, echocardiographic study. Am Heart J 119:1402, 1990; with permission.)

the IAS was 6 mm, although the range was large (2–20 mm). The average thickness of the septum in the fossa ovalis was 1.8 mm.[83] There is a significant thickening of the IAS during atrial systole.[70, 83] The septum is a bladelike structure with three margins when viewed from the right atrium (Fig. 4). The posterior margin is defined superiorly by its junction with the superior vena cava and inferiorly by its junction with the coronary sinus. The anterior margin is defined superiorly by the medial side of the orifice of the superior vena cava and inferiorly by the fibrous trigone just posterior to the membranous interventricular septum. The inferior margin extends from the coronary sinus to the trigone.[93] The oval-shaped fossa ovalis is located just over halfway between the superior and inferior margins of the IAS.

When viewed from the left atrium (Fig. 5), the anterior margin of the IAS follows the curvature of the posterior wall of the ascending aorta. The posterior margin forms a convex curve that runs just medial to the entry of the right pulmonary veins. The inferior margin is formed by the medial portion of the mitral valve annulus.

Atrial Septal Abnormalities

Atrial Septal Defect

Atrial septal defect (ASD) is among the most common congenital defects of the heart. It is the principal lesion in approximately 15% of all patients with congenital heart disease who survive infancy.[67] There are three types of ASDs based on the anatomic site of the defect (Fig. 6).

Ostium Secondum ASD. This defect, which accounts for 70% of ASDs, is caused by maldevelopment of the septum secundum or the septum primum. It occurs either as a single defect or as several smaller

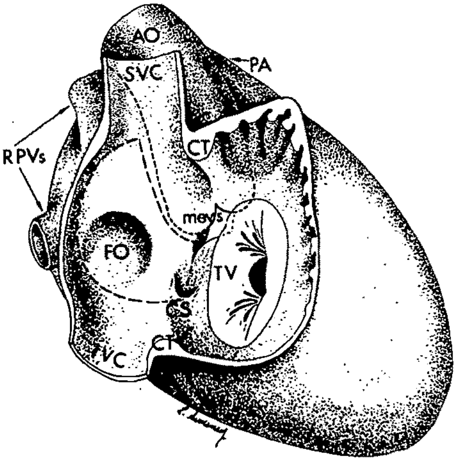

Figure 4. Right atrial view of the normal atrial septum (*heavy broken line*). Position of the aorta is indicated by light broken line. CS = coronary sinus; CT = crista terminalis; FO = foramen ovale; IVC = inferior vena cava; SVC = superior vena cava; mevs = membranous ventricular septum; PA = pulmonary artery; RPV = right pulmonary vein; TV = tricuspid valve. (*From* Sweeney LJ, Rosequist GC: The normal anatomy of the interatrial septum—development and clinical significance. Am Heart J, 98:194, 1979; with permission.)

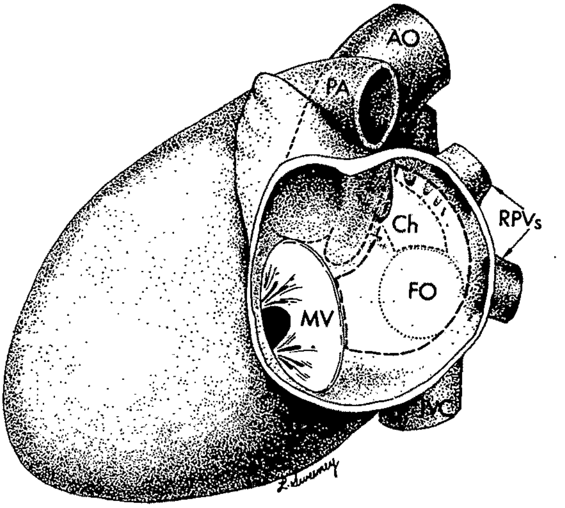

Figure 5. Left atrial view of normal atrial septum (*heavy broken line*). Dotted line outlines fossa ovalis; light broken line outlines margins of the ascending aorta and persistent channel (Ch) of the foramen ovale. MV = mitral valve; AO = aorta; FO = foramen ovale; PA = pulmonary artery; RPVs = right pulmonary veins. (*From* Sweeney LJ, Rosequist GC: The normal anatomy of the interatrial septum—development and clinical significance. Am Heart J, 98:194, 1979; with permission.)

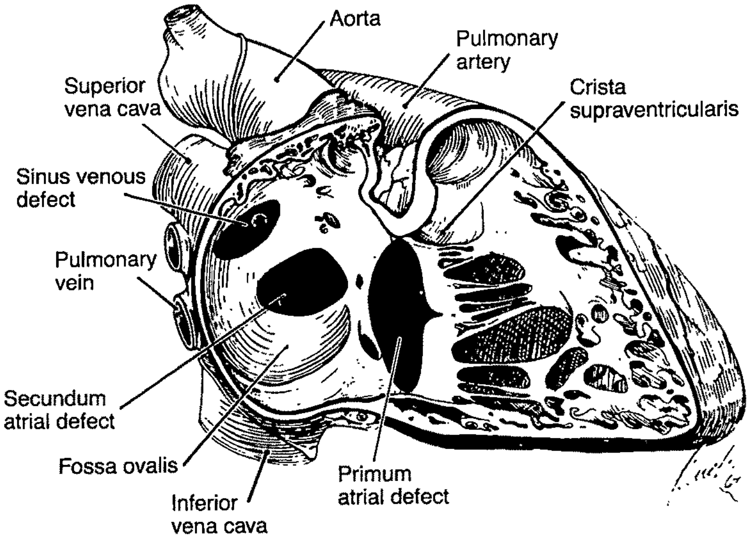

Figure 6. Composite locations of atrial defects. (*From* Braunwald E (ed): Heart Disease—A Textbook of Cardiovascular Medicine. WB Saunders, 1988.)

openings in the septum secundum and is located in the region of the fossa ovalis. The size of the defect varies greatly, from tiny cribriform openings to virtual loss of the entire septum secundum.

Ostium Primum ASD. This is a defect in the inferior border of the atrial septum due to failure of the septum primum to fuse normally to the endocardial cushions, which usually form the floor of the atria. Primum defects, which account for 15% of ASDs presenting in the adult, can vary in size from absence of the inferior portion of the septum immediately adjoining the atrioventricular valves to virtually complete absence of the septum (common atrium).

Sinus Venosus ASD. This type of defect occurs high in the roof of the atrium and is usually associated with anomalous pulmonary venous return from the right upper and middle lung fields. It represents about 15% of ASDs presenting in the adult.

Patent Foramen Ovale

During the first year of life, fibrous adhesions usually develop between the septum secundum and the septum primum, forming an anatomic seal of the foramen ovale. However, in a substantial percentage of people, the foramen ovale does not seal completely and, therefore, a potential interatrial channel remains. A patent foramen ovale (PFO) is the most common component of the fetal circulation to persist beyond the neonatal period. Estimates of its incidence vary depending on the age range of the subjects involved and on whether associated congenital heart disease is present. Table 1 indicates a 25% to 35% incidence of PFO in heart specimens without other congenital lesions. In an autopsy study of 965 such specimens, Hagen et al[33] found that neither the incidence nor the size of the defect differed significantly by race or sex. The overall incidence of PFO was 27.3%, but there was a progressive decline with subject age from 34.3% in the first three decades to 25.4% during the fourth through eighth decades of life to 20.2% during the ninth and tenth decades. The mean size of the defect

Table 1. INCIDENCE OF PATENT FORAMEN OVALE (PFO) IN VARIOUS STUDIES

Year	Authors	No. of Hearts	Incidence of PFO (%)	Age (yr) of Patients
1897	Parsons and Keith	399	26	All ages
1900	Fawcett and Blachford	306	31.7	>10
1918	Scammon and Norris	1809*	29	>1
1931	Patten	4083*	24.6	Mostly adults
1934	Seib	500	17	>20
1948	Wright et al	492	22.9	Mostly adults
1972	Schroeckenstein et al	144	35.4	>20
1979	Sweeney and Rosenquist	64	31	>10
1984	Hagen and Scholz	965	27.3	>1

*Combined review of literature.

From Hagen PT, Scholz DG, Edwards WD: Incidence and size of the patent foramen ovale during the first 10 decades of life: An autopsy study of 965 normal hearts. Mayo Clin Proc 59:17, 1984; with permission.

was 4.9 mm in this study, with a range of 1 to 19 mm and with 98% of patients having defects less than 10 mm in diameter. Thus, late closure of the foramen ovale apparently occurs in a significant number of persons. In studies of hearts with PFO and coexistent congenital or acquired abnormalities, there is no age-associated decrease in the incidence of PFO, suggesting that coexistent cardiac disease favors maintenance of foraminal patency.

In most studies, the incidence of PFO as diagnosed by in vivo imaging techniques is far lower than that found in autopsy studies. This results from two facts: Probe patency connotes only the *potential* for communication and the available imaging techniques are not 100% sensitive.

Atrial Septal Aneurysm

This previously obscure entity has been extensively studied since the advent of two-dimensional and transesophageal echocardiography. The reported incidence of atrial septal aneurysm (ASA) is about 1% in autopsy studies[88] and about 0.2% in echocardiographic studies.[34]

When the region of the septum primum underlying the fossa ovalis bulges into either atrium, a fossa ovalis or ASA is present.[5] All aneurysms of the atrial septum involve the fossa ovalis region.[74] In the normal heart, this region may be slightly redundant and wrinkled.[88] Unlike a true ASA, however, this normal variant cannot be displaced far into either atrium.[5]

ASAs have been classified as primary or secondary, although this classification has been challenged. In theory, secondary ASAs develop as a consequence of an excessive pressure difference between the atria, most commonly as a result of congenital heart disease. However, ASAs are not seen in the vast majority of cases of congenital heart disease in which there is a large atrial pressure differential; also, they are equally common in children and adults. These facts suggest that most of these aneurysms are primary and cannot be attributed solely to an atrial pressure differential.[34] However, they are unusual as isolated entities and are most commonly seen in association with secundum ASD.[16]

The echocardiographic definition of ASA requires the following: (1) All or part of the atrial septum exhibits dilation (protrusion greater than 1.5 cm beyond the central plane of the septum) and manifests phasic excursion of greater than 1.5 cm during the cardiorespiratory cycle; and (2) the base of the aneurysmal part of the septum is greater than 1.5 cm in diameter. Atrial septal aneurysms can also be subdivided into two anatomic subsets: those in which the aneurysm involves only the region of the fossa ovalis and those in which the entire atrial septum is involved. Fossa ovalis–type ASAs are by far the more common (about 90%).

While the pathogenesis of ASA is unknown, there is a documented association between ASA and mitral valve prolapse.[74] A common underlying congenital defect in connective tissue resulting in redundancy of endocardial tissue has been proposed.[74]

PHYSIOLOGY AND PATHOPHYSIOLOGY

Atria

The right atrium (RA) receives venous return from the superior vena cava, the inferior vena cava, and the coronary sinus. Pressure waveforms within the RA have been well described. There are two major positive pressure peaks in the waveform: the A and V waves (Fig. 7). The A wave is caused by atrial systole. After atrial systole, there is a decline in pressure within the RA, which creates a descent in the pressure trace (the X descent) from the peak of the A wave. Toward the end of the X descent, a small positive deflection results from ventricular systole and closure of the tricuspid valve. This is called the C wave. Following the C wave, RA pressure continues to fall even though the atrium is filling with blood (the atrial musculature is relaxing). With continued filling of the RA, pressure again begins to rise, resulting in the V wave, which occurs just before the opening of the tricuspid valve. After this valve opens, the right atrial pressure decreases, creating the Y descent in the pressure tracing. At the nadir of the Y descent, the right atrial and right ventricular pressures are equal and both increase slowly as the ventricle fills. Simultaneous pressure and volume curves for the RA have been measured in normal subjects (Fig. 8).

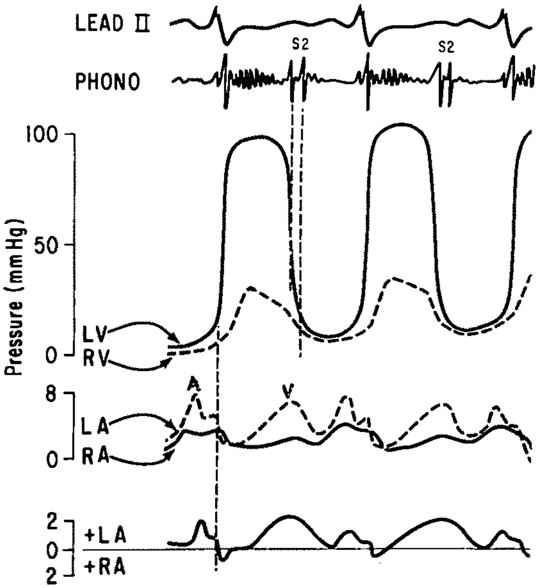

Figure 7. Intracardiac pressure dynamics in secundum atrial septal defects. All data were recorded simultaneously with the lead II electrocardiogram and a phonocardiogram in the left second interspace (*From* Levin AR, Spoch MS: Atrial pressure flow dynamics in atrial defect (secundum type). Circulation 37:476, 1968; with permission.)

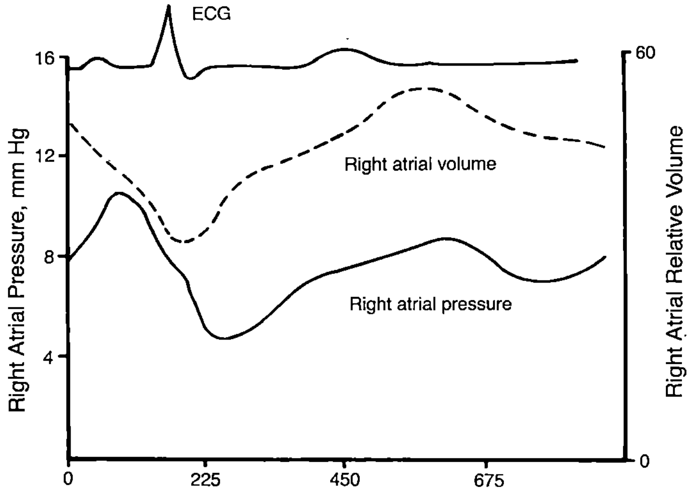

Figure 8. Simultaneous right atrial baseline pressure and volume signals from a patient with normal coronary arteries and no atrial septal defect. The ECG tracing is shown for timing purposes. The abscissa (time) is in milliseconds. (*From* Ferguson JJ III, Miller MJ, Aroesty JM, et al: Assessment of right atrial pressure-volume relationships with and without an ASO. J Am Coll Cardiol, 13:630, 1989; with permission.)

Respiration causes characteristic changes in filling dynamics. Inspiration causes a decrease in RA pressure and an increase in RA volume. In contrast, during expiration, mean RA pressure rises while RA volume falls. During the strain phase of the Valsalva maneuver, RA pressure increases while RA volume falls.[25]

The left atrium (LA) receives venous return from the pulmonary veins. Pressure waveforms in the LA are also well described, both by recording directly from the LA or by indirect transmission via the pulmonary capillary bed (pulmonary artery wedge position [PAWP]). The LA pressure profile also shows A, C, and V waves associated with the same flow phenomena and timing as seen in the RA. The PAWP tracing shows similar waves except that they are somewhat delayed and damped owing to retrograde transmission through the pulmonary vessels to the PAWP catheter. The LA is not as directly susceptible to respiratory cycle–based pressure and volume changes as is the RA. The strain phase of the Valsalva maneuver affects the LA pressure and volume but mainly indirectly; that is, LA volume decreases secondary to the decreased pulmonary flow caused by less right heart filling.

Because it is less compliant than the RA, LA pressure is normally greater than RA pressure throughout diastole, with the maximal pressure difference occurring at the peak of the V wave.[42] However, when the atrioventricular valves are closed at the onset of ventricular contraction, there is a more prominent fall (X descent) in LA than in RA pressure, resulting in a transient period of reversed gradient (Fig. 7).[51] This phenomenon may result from the movement of the base of the ventricles, which produces greater fluctuations in LA pressure than in RA pressure.[100]

Differences in pressures between the two atria are accentuated during phases of increasing intrathoracic pressure[51] as a result of a brief rise in RA pressure while a corresponding rise in LA pressure. The RA is apparently more sensitive to abrupt changes in intrathoracic pressure, and therefore RA pressure undergoes a more pronounced rise than LA pressure while intrathoracic pressure is increasing. However, when the intrathoracic pressure reaches a plateau, systemic venous inflow to the RA decreases, with a resultant decrease in cardiac volume, and the pressure difference between the atria is minimized.

Interatrial Septum (IAS)

Echocardiographic analysis of IAS motion has been studied with M-mode and two-dimensional echocardiography.[94] It was found that IAS motion was maximal at its midportion and decreased gradually toward the periphery. The IAS changed its shape throughout the cardiac cycle, as it was convex toward the RA at mid- and end-systole and in early diastole and was flat or convex toward the LA in mid- and end-diastole and in early systole. Simultaneous pressure measurement showed that the motion of the IAS was driven by the interatrial pressure difference. Thus, the IAS is a flexible, dynamic membrane; its motion is responsive to relative atrial hemodynamics (Fig. 9).

As previously discussed, with atrial septal aneurysm (ASA) there is a bulging of the IAS into either atrium. The motion of the aneurysmal IAS usually follows the motion pattern of the normal IAS, albeit somewhat exaggerated. The ASAs that exhibit greater phasic motion are most likely to be associated with an interatrial communication, such as a PFO or an ASD.[34] An interatrial communication probably predisposes the ASA to increased mobility, because interatrial blood shunting produces more similar RA and LA pressures, and interatrial pressure gradient reversal during the cardiac cycle is therefore more common. There also may be flow-related pressure gradients (Venturi effect) adjacent to the ASA that cause septal motion.

Interatrial Septal Communications

Initially, it was believed that the predominance of left to right shunting associated with sizable IAS communications was due to the more superior position of the LA compared to the RA, leading to a "gravitational" shunt.[96] However, subsequent work suggested that the direction of the shunt resulted from the higher compliance of the right ventricle relative to the left ventricle and of the right atrium relative to the left atrium.[10, 40] The timing of shunt flow was also debated, and it was suggested that flow through the communication occurs throughout

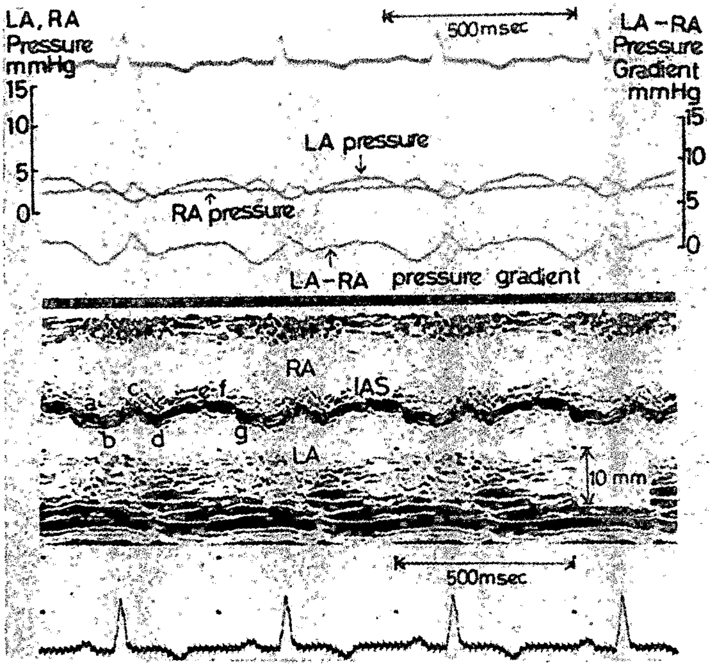

Figure 9. Left (LA) and right (RA) atrial pressure curves, left-to-right (LA-RA), interatrial pressure gradient curve (*upper panel*), and interatrial septal (IAS) echogram (*lower panel*), recorded in an open chest dog. The upper and lower records were obtained simultaneously. The septal echocardiographic curve is very similar to the pressure gradient curve. (*From* Tei C, Hiromitsu T, et al: Echocardiographic analysis of interatrial septal motion. Am J Cardiol 44:472, 1979; with permission.)

the cardiac cycle. A study performed in 1968 on a series of patients with ostium secundum ASDs correlated left and right atrial pressure measurements with cineangiographic dye flow across the defect.[51] It was found that the major pressure gradient and shunt from LA to RA occur over an interval encompassing late ventricular systole and early diastole, with augmentation during atrial systole. Minute but definite right to left shunting occurred at two times during the cardiac cycle: with the onset of ventricular contraction and during early diastole (see Fig. 7).

In patients with an ASD, baseline pressure-volume diagrams are normal, but there are sharp alterations in the respiratory variation.[25] There is no change in RA volume associated with respiration, as the normal changes in venous return to the RA that occur during the respiratory cycle are balanced by an opposite change in the magnitude of the intracardiac shunt. It is for this reason that a pulsus paradoxus cannot usually be demonstrated in the presence of an ASD.

Right to left shunting of blood occurs in association with all interatrial communications regardless of right ventricular function or pulmonary artery pressure. Depending on the analytic technique used, the proportion of patients with RA to LA shunting in the presence of an ASD has been reported to be from 15% to 100%.[42] However, the shunt volume may be miniscule. A study using oximetric analysis in 40 patients with uncomplicated ASD showed that 6 of these patients had significant volume shunts from RA to LA.[1] Studies using dye dilution,[92] fiberoptic catheters,[28] intracardiac Doppler,[46] and transthoracic echocardiographic techniques[84] have confirmed the presence of right to left shunting in uncomplicated ASD, albeit with varying incidence.

In the newborn and the infant, fetal hypertrophy of the RA and right ventricle tends to prevent a left to right shunt. This may explain the rarity with which ASD presents clinically in these age groups. After infancy, the hypertrophy of the right side of the heart regresses, resulting in the predominantly LA to RA shunt seen in adults. If the shunt is large enough, the RA and RV dilate from the increased volume. Over time, these chambers become less compliant, resulting in an increase in the degree of right to left shunt.[42] No such evolution would be expected in small ASDs or in other IAS communications, as the shunt volume is too small to produce these changes in the right heart chambers.

As previously discussed, the Valsalva maneuver produces a marked decrease in RA volume during the plateau of the strain phase, because of a decrease in venous return to the RA secondary to increased intrathoracic pressure. In patients with an ASD, there is no change in RA volume during the strain phase, because of an augmentation of left to right shunt flow at this time. Release of the strain is associated with sudden augmentation of RA filling and, as confirmed echocardiographically, can result in the development of an RA to LA shunt.

Changes in body position significantly alter cardiopulmonary function. Two events occur when a patient with an IAS communication shifts from a supine to an erect posture[73, 75, 85]:

1. There is an increase in pulmonary vascular impedance relative to the systemic circuit, which may act to increase RA to LA shunting. This has been demonstrated using a tilt table in patients with a PFO.
2. There is a change in the position of the atria relative to one another. By placing the LA in the dependent position, and thereby increasing the gravitational hydrostatic force, the degree of RA to LA shunting may increase. This effect may also explain the decrease in oxygen saturation that may occur with the patient in the left lateral decubitus position. These factors must be considered during surgery in the sitting position in which many of these patients have an RA pressure greater than that in the LA.[72]

In both anesthetized[17] and unanesthetized[32] patients, positive pressure ventilation was observed to provoke RA to LA shunting, principally immediately following release of airway pressure, probably as a result of a sudden increase in RA filling. Whether peak airway pressure and frequency or volume of shunting are related is unclear.[23]

There are conflicting reports on the influence of positive end expiratory pressure (PEEP) on relative atrial dynamics.[4, 49] Whereas one report showed a significant increase in RA pressure and no change in PAW pressure in seated patients with neurologic disease receiving 10 cm H_2O PEEP, a second report in a similar population showed that PAW pressure increased to the same extent as the RA pressure.

There have been several case reports of dyspnea associated with new right to left atrial shunting following pneumonectomy, usually of the right lung.[81, 102] Shunts have been reported across PFOs or secundum ASDs. Pulmonary and right atrial pressures are usually normal and the condition may not appear until several weeks postoperatively, excluding positional influence. The shunt seems to be dominated by blood from the inferior rather than the superior vena cava, suggesting a directional or "streaming" effect. Presumably, there is an alteration in the anatomic position of the IAS after pneumonectomy that allows previously undetected defects to become clinically significant.[38] The dominance of the inferior vena cava inflow may be related to a persistent eustachian valve, which aids in directing blood from the inferior vena cava to the LA via the foramen ovale, as it does in the fetal circulation. Surgical procedures other than pneumonectomy that result in postoperative mediastinal distortion have also been reported to result in significant right to left atrial shunts.[38]

There are reports of hypoxemia unresponsive to high concentrations of oxygen during emergence from anesthesia. This event is seen mainly in infants and children, the age group with the highest incidence of IAS communication.[57, 62, 103] During the early phases of emergence from anesthesia, patients cough and strain and ventilation may be difficult. Hypoxemia occurring at this time, however, may not be only due to problems with ventilation. During straining and coughing, RA pressure increases as a function of increasing intrathoracic pressure. This may lead to a right to left shunt through a preexisting IAS communication. As will be discussed in detail in a later section, it is at this time that such patients are at risk for systemic embolization of air inadvertently introduced via an intravenous infusion. The phenomenon may be only transient, often occurring when difficulty with patient behavior on the ventilator could easily explain the hypoxemia, and thus may not be appreciated unless a high level of suspicion is maintained.

An increase in pulmonary artery pressure acutely or chronically can also substantially alter right ventricular filling dynamics and compliance. These changes may be transmitted to the right atrium and may result in RA pressure equaling or exceeding LA pressure, accentuating RA to LA shunting.

The pressure gradient and flow across an IAS communication are greatly affected by other conditions that alter right ventricular compliance. For example, there are several reports of interatrial shunting and profound hypoxemia resulting from a large right ventricular infarction, as well as following coronary artery bypass grafting.[52, 77] Extrinsic forces can also play a role in changing the behavior of an IAS communication.

In one case report, cardiac tamponade secondary to an aortic dissection resulted in a decrease in blood flow through a very large secundum ASD.[63] The tamponade caused equalization of right and left ventricular compliance, thus decreasing the net shunt flow. However, focal limitation, as seen in constrictive pericarditis, can result in shunt flow in either direction depending on the chamber more affected by the extrinsic compression.[11] In a case report describing postoperative constrictive pericarditis and an associated PFO,[48] significant RA to LA blood flow resulted from increased RA pressure caused by right ventricular diastolic compression.

Mitral valve disease in association with interatrial communication and shunting is rare.[58] The first comprehensive description of the syndrome of mitral stenosis and ASD was published in 1916 by Lutembacher.[56] As would be expected, the degree of shunting and thus the severity of complications of the ASD, including pulmonary hypertension, vary with the size of the ASD and the severity of the mitral stenosis. The presence of a large ASD may mask the signs and symptoms of severe mitral stenosis for years, as the interatrial communication acts as a decompression channel for the LA.[3]

INTERATRIAL COMMUNICATION AND SYSTEMIC EMBOLISM

Systemic embolization via an intracardiac right to left communication was first described by Cohnheim in 1877.[15] The term *paradoxical embolism* describes an entity that requires the presence of four conditions.

Thrombus Must Be Present in the Venous System. Embolism in the presence of atrial septal communication is mainly paradoxical. This is a testimony to the fact that the venous system is much less dynamic than the arterial. Blood in the veins is driven by inconstant muscle contraction and gravity rather than under high, pulsatile pressure. An elaborate system of venous valves aids in transport. The right heart operates under low pressure and can be viewed as a relatively passive conduit to the lungs. Thus, the venous system has only a small margin of safety against stasis, which may allow thrombus formation. In fact, thrombus formation (and dissolution) must be a regular occurrence in a normally functioning venous system. Sizable venous thrombosis and embolization is often occult: even in patients with pulmonary thromboembolism, a clinical diagnosis of deep vein thrombosis (DVT) can be made in less than 50% of cases. By far, the majority of clinically significant embolic events originates in the venous circulation.

An Abnormal Communication Must Exist Between the Right and Left Circulations. The incidence, anatomy, and physiology of IAS communications have been discussed in detail. A PFO is a common entity and there have been numerous reports documenting its presence in the setting of a systemic embolic event. However, any interatrial communication can participate in the development of systemic embolism.

Clinical, Angiographic, or Pathologic Evidence of Systemic Embolism Must Be Present. Systemic embolic events are often clinically silent. Cerebrovascular accident (CVA) is an obvious and devastating clinical sequela of systemic embolization and it is the entity that has generated most of the investigation of PFO. Serious clinical syndromes are also associated with coronary or peripheral arterial embolization. Other systemic embolic events (e.g., splenic, intestinal, hepatic) may be asymptomatic or associated with nonspecific symptoms that resolve spontaneously and are thus frequently not detected.

A Pressure Gradient that Promotes Right to Left Shunting Must Exist at Some Time in the Cardiac Cycle. As we have seen, pressure in the RA exceeding that in the LA is a normal event during the cardiac cycle. Thus, most interatrial communications allow right to left flow during some part of the cycle. Other conditions that impact on the relative atrial dynamics often make the right to left flow more prolonged and more severe.

Until 1930, paradoxical embolism could only be recognized at autopsy.[54] With the advent of newer imaging modalities, the accurate diagnosis of paradoxical embolism in the living patient has been greatly facilitated.[14, 39, 50, 60, 90] The development of two-dimensional echocardiography over the past decade, in association with Doppler echocardiographic techniques, has greatly enhanced the evaluation of the interatrial septum in the presence of systemic embolization. The more recent advent of transesophageal echocardiography (TEE) has provided a direct window to the IAS.[13, 36, 65, 86]

An incorrect diagnosis of paradoxical embolism may be made if another source of embolus is not appreciated. For example, a patient with paroxysmal atrial fibrillation may have a systemic embolic event originating from a thrombus in the left atrial appendage. Evaluation by a transthoracic echocardiogram frequently does not show the thrombus, yet a PFO may be seen, which might then be incorrectly implicated. Other potential sources of embolism that should be considered include LV thrombus, atrial myxoma, valvular vegetation, mitral valve disease, and atherosclerosis leading to atheromatous or thrombotic emboli.

It is difficult to make the diagnosis of paradoxical embolism with absolute certainty during life given the frequent occurrence of PFO. A paradoxical embolism via an interatrial communication may be considered to be proven when a venous thrombus is found lodged within a septal defect at necropsy in a patient who has had a systemic embolic event.[43] There have been rare reports during life of biatrial, or "straddling," thrombi across an interatrial communication in the setting of systemic or pulmonary embolization.[54] This phenomenon has been diagnosed by transthoracic echocardiography[69] or TEE[68] (Fig. 10).

There are several intracardiac connections that should be considered in patients with true paradoxical embolization. In one review of 25 cases of paradoxical embolism, 18 were associated with PFO, 3 with ASD, 3 with pulmonary arteriovenous fistulae, and 1 with a ventricular

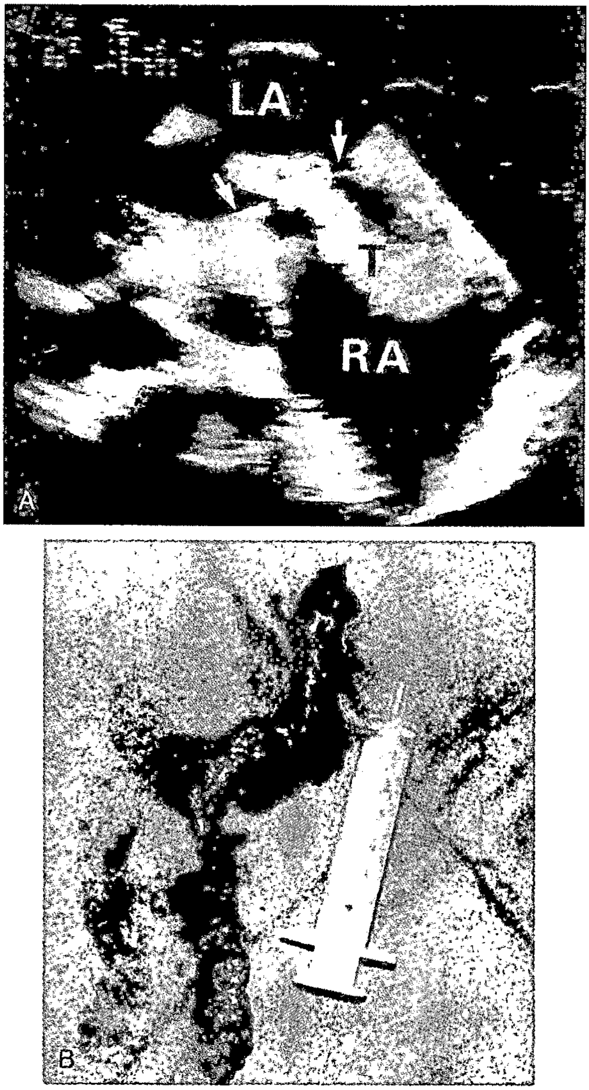

Figure 10. *A*, Transesophageal two-dimensional echocardiogram showing a thrombus (T) in the left (LA) and right (RA) atria overriding the interatrial septum (*arrows*). *B*, Surgical specimen of the atrial thrombus shown in *A*. (*From* Nellessen U, Daniel WG, Matheis G, et al: Impending paradoxical embolism from atrial thrombus: Correct diagnosis by transesophageal echo and prevention by surgery. J Am Coll Cardiol 5:1002, 1985; with permission.)

septal defect.[54] Of note, a large proportion of these patients also had had clinically documented pulmonary emboli, whereas a somewhat smaller number also had a diagnosis of deep venous thrombosis. Patients with a PFO who subsequently underwent cardiac catheterization did not manifest oximetric evidence of a significant shunt.

In several cases, systemic embolization occurred during periods in which an RA to LA pressure gradient would have been expected, such as following pulmonary embolism or during a Valsalva maneuver.

The frequency of interatrial communications and the rarity of the syndrome of paradoxical embolism make it difficult to prove the role of the interatrial communication in patients with a systemic embolic event, although the circumstantial evidence is compelling. In a study of 127 patients, Caplan et al[12] demonstrated that about 40% meeting strict criteria for an embolic CVA had no identifiable intracardiac or arterial source. This incidence is about 50% in younger age groups.[29] However, these studies did not use techniques that specifically look for an intracardiac communication. Several reports of embolic CVA not associated with a clear source have shown an association with an IAS communication, usually a PFO.[44, 98] Lechat et al[49a] studied the prevalence of PFO in a population of 60 adults younger than age 55 who had had a cerebral infarction. The incidence of PFO, as diagnosed by contrast echocardiography, was four times greater in the patients with CVA than in age-matched healthy control subjects. The prevalence of PFO in the group with another identifiable cause of the CVA was 21% and was 54% in patients who had no other identifiable cause for the CVA. One small series of 11 patients younger than age 50 with unexplained cerebral embolism identified 8 with evidence of a right to left shunt at the atrial level during normal respiration.[35] In another study of 66 patients younger than 40 years of age with a transient ischemic attack (TIA) or nonhemorrhagic CVA, the prevalence of PFO was found to be 50% using contrast echocardiography with provocation by the Valsalva maneuver compared with 15% in a control group.[98] The patients with CVA and a PFO also had more severe shunting than those in the control group with PFO. Thirteen of 18 reported cases of paradoxical coronary arterial embolization were associated with a PFO; 4 other patients had an ASD, including 3 with documented right to left shunts.[8, 14, 37, 41, 45, 53, 79, 90, 99] In 10 cases, the coronary embolism followed a pulmonary embolic event.

The results of other studies that determined the incidence of ASD and PFO by using newer techniques (TEE and color flow Doppler) in patients with and without systemic thromboemboli suggest a strong association between interatrial communication and systemic thromboembolic events in otherwise normal hearts.[18, 66, 91] This, however, does not establish IAS communication as critical to the embolic mechanism.

Reports associating systemic embolism with IAS communications have not been limited to thromboembolism. For example, systemic air embolism may occur during certain operations, including neurosurgical procedures performed in the sitting position.[30]

As previously discussed, positive pressure mechanical ventilation increases RA pressure, potentially increasing the incidence of right to left shunting at the atrial level in the presence of a PFO. The addition of PEEP may further enhance this effect. The effects of different patterns of ventilation and intravascular volume infusion on the occurrence of paradoxical air embolism in pigs with a surgically created ASD have been studied.[9] With the animals in a head-up position, air was infused into the superior vena cava for 6 minutes or until air embolization was noted. Four situations were studied: (1) intermittent positive pressure ventilation (IPPV), (2) IPPV with 10-cm H_2O PEEP, (3) spontaneous ventilation, and (4) IPPV following 500 mL of intravenous hetastarch. The incidence of air embolism did not differ in any of the groups and was similar whether the mean LA pressure was less or greater than the mean RA pressure. However, release of PEEP resulted in the development of air embolism or an increase in its severity, because of a sudden increase in systemic venous return at that instant, raising RA pressure at a time when venous return to the LA remained relatively low. It is important to emphasize that although maintenance of PEEP probably does not alter the interatrial pressure gradient, a change in the level of PEEP may increase the possibility of paradoxical air embolization.

An interesting relationship between decompression sickness and systemic embolism has been observed in divers. During and after rapid ascent, a diver may suffer decompression sickness and pulmonary barotrauma.[22] During decompression, bubbles of gas (nitrogen if the diver is breathing air) are liberated from body tissues. These bubbles can be detected in venous blood, and their passage from the right to the left heart via an IAS communication may result in the neurologic symptoms that are a common manifestation of decompression sickness.[20] In a case report of cerebral and spinal cord decompression sickness in a scuba diver who subsequently proved to have an ASD, it was concluded that the patient had had systemic embolization as a result of venous gas emboli passing through the ASD.[101] In a larger study of 30 patients with a history of decompression sickness, mostly in association with sports diving, a significant relationship with the presence of IAS communication was demonstrated.[61] The severity of the clinical syndrome was also significantly correlated with the presence of a communication; a PFO was demonstrated in 61% of the patients with a history of severe decompression sickness. It has thus been demonstrated that an increase in hydrodynamic pressure on the body, as occurs with submersion, increases RA pressure, creating a more favorable environment for transseptal shunting.[2]

Other types of material have been reported to embolize via the atrial septal route. For example, septic embolization to the brain has been reported from a tricuspid valve vegetation via a PFO.[87] Tricuspid regurgitation resulted in elevation of the RA pressure. Right to left shunting through the coexisting PFO was demonstrated by contrast echocardiography. Systemic embolization with fat, tumor, or amniotic fluid can also occur. However, there is little information to suggest a relationship between the occurrence or severity of these syndromes and the presence of an IAS communication.

As previously discussed, the diagnosis of atrial septal aneurysm

(ASA) includes a spectrum of abnormalities of the IAS from localized dilation of the fossa ovalis to involvement of the entire IAS. In recent years, it has been recognized that this entity is associated with embolic stroke, coronary arterial embolism, and pulmonary arterial embolism.[31, 95, 105] The embolic potential of an ASA has been supported by the finding at necropsy of thrombus at its base,[88] by histologic evidence of organized thrombus within a resected ASA,[31] and by transesophageal echocardiographic demonstration of thrombus within an ASA.[82] However, in many patients, there are associated disorders, such as mitral valve prolapse, valvular heart disease, or atrial arrhythmias, each of which is independently associated with systemic embolic events.[27, 97] In addition, interatrial communication is common with ASA. Studies employing transthoracic and transesophageal echocardiography have demonstrated that one third to one half of patients with an ASA have an associated PFO or ASD.[6, 19, 88] Thus, while there may be an independent role of the ASA in systemic, and possibly pulmonary, embolization, coexisting lesions, especially IAS communication, may be involved in many cases.

IMAGING OF INTERATRIAL COMMUNICATIONS

Prior to the advent of echocardiography, direct visualization of atrial septal anatomy was possible only postmortem or during surgery; septal communications could be diagnosed only indirectly. Shunts of hemodynamic significance were detectable by oximetry during cardiac catheterization. Smaller shunts could be detected by techniques such as hydrogen arrival and indicator dilution. However, the sensitivity of some of these methods in the presence of an IAS communication with minor or intermittent shunting may be low. Two-dimensional echocardiography, especially with more recent advances in image resolution and with the development of Doppler techniques, has revolutionized the morphologic and functional evaluation of the IAS. Morphologic evaluation of the atrial septum by two-dimensional echocardiography is useful in the assessment of overt structural abnormalities such as large ASDs or ASAs. For smaller or intermittent communications, analysis with flow-based techniques is necessary. Transthoracic Doppler echocardiography, including the color flow technique, has been used with some success in the diagnosis of interatrial shunting.

Contrast two-dimensional transthoracic echo has been of enormous use in the evaluation of small IAS communications. This technique is based on the use of an echo-detectable contrast material, most commonly the microbubbles produced by agitating an injectable fluid such as saline or albumin. Rapid injection of this material into a peripheral vein leads to prompt echo opacification of the RA and RV. In the presence of an interatrial communication, contrast is seen in the left heart within one to four beats of injection, thus excluding transpulmonary passage as a mechanism. Maneuvers designed to change the RA-LA pressure gradient, such as the Valsalva maneuver or cough, are used during the contrast injection in order to enhance detection of an interatrial communication.

Results with the contrast technique are excellent with sensitivity and specificity as high as 100% and 80%, respectively.[24] The procedure is safe with only scattered reports of deleterious effects.[37] Contrast echo provides only a qualitative assessment (i.e., positive or negative); quantitative analysis of the degree of shunt by this method is not reliable.

The development of the transesophageal approach has produced an almost perfect window on the structure and function of the IAS because of the proximity of the atria to the esophagus and of the fact that the transducer faces the IAS nearly perpendicularly.[59] The Doppler technique permits quantitative as well as qualitative assessment of interatrial shunting with remarkable sensitivity and specificity[64] (Fig. 11). The recently developed biplane transducer offers imaging in a second plane, affording an even more precise anatomic diagnosis.

The diagnostic capability of TEE is superior to that of transthoracic

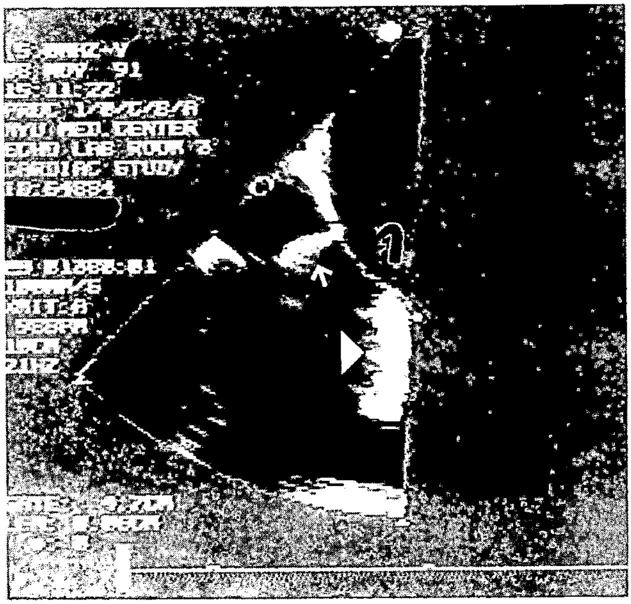

Figure 11. Color Doppler imaging of the aorta and interatrial septum using the transesophageal echocardiogram. The IAS is indicated by the curved black arrow. Above is the LA, below is the RA. Two interatrial communications are seen: a large one *(solid white arrowhead)*, and a smaller one *(regular white arrow)*. Flow is from the left atrium to the right, as indicated by the white areas. Note also bowing of the IAS, in a left-to-right direction, indicating LA pressure greater than RA pressure at the moment the picture was taken. (Courtesy of Itzhak Kronzon, MD, New York University School of Medicine, New York, NY.)

echocardiography; a three to five fold increase in the diagnosis of PFO is noted with the former technique.[18, 71] A similar superiority of TEE has been documented for detection of ASA and for nonoperative diagnosis of thrombus involving an ASA.[82] Even with TEE, however, color Doppler techniques have limitations in detecting IAS communications because of their relatively low flow velocities, especially if flow periods are brief. However, the use of contrast in association with TEE can overcome these problems. In a study that compared TEE contrast to TEE color flow Doppler in the assessment of PFO, a fourfold increase in yield for contrast over TEE with color flow mapping was found.[89]

Newer echocardiographic techniques are being used to explore IAS communications. Intravascular ultrasound consists of a two-dimensional echocardiographic transducer mounted on a catheter that can be directed into the heart. It has allowed accurate size and shape estimation of ASDs, including changes associated with various maneuvers and at various times in the cardiac cycle.[78]

Among other imaging techniques, intravenous digital subtraction angiography (DISA) is a relatively noninvasive method that provides cardiac images with a spatial resolution comparable to that of contrast angiography. This technique has been utilized to detect the presence of ASA[105] and left to right shunts[104] as well as for shunt quantitation. The shortcomings of this technique are similar to those described for cardiac catheterization.

Magnetic resonance imaging (MRI) shows a density contrast between the blood pool and cardiac structures because of the absence of a signal from blood flowing at normal velocities. Therefore, it permits noninvasive evaluation of the cardiovascular system without the use of contrast agents or ionizing radiation. MRI with electrocardiogram gating has been effective in demonstrating atrial septal defects.[55] In a study that used gated cardiac MRI in 31 patients with known ASD and in 33 normal subjects, 97% of ASDs were accurately identified with high specificity.[21] However, given the predominance of PFO, MRI, which is a morphologic rather than a flow technique, would be expected to have serious shortcomings, as the PFO is not associated with a significant anatomic defect.

It is of critical importance in the diagnosis of most IAS communications to have a technique capable of visualizing the septum over a significant period of time, during various maneuvers, and in association with methods that allow detection of even subtle flow. At present, contrast TEE is the best available diagnostic tool.

CLINICAL IMPLICATIONS

Several features of the IAS and its association with systemic embolization are apparent:

1. IAS communications are extremely common.

2. All IAS communications can result in shunting of blood in a right to left direction regardless of the hemodynamic significance of the communication or associated cardiac abnormalities.
3. IAS communications are associated with systemic thromboembolic events and probably with systemic air emboli.
4. Atrial septal aneurysms are probably associated with both systemic and pulmonary thromboembolism, although the association is tenuous given the frequent concomitant presence of an IAS communication.
5. Certain operative procedures are associated with the possibility of venous air entrainment, and patients who have IAS communications are at risk of air embolization to the systemic circulation during such surgery. Certain hemodynamic and ventilatory maneuvers are likely to increase both the risk and the magnitude of right to left shunting.

Any recommendations for intervention following systemic thromboembolism are necessarily tempered by the prevalence of IAS communication or ASA. Also, given the small numbers of patients in controlled studies, especially of those suffering recurrent embolic events, it is difficult to draw conclusions about natural history and to make reasonable recommendations. Although there are no guidelines, management issues in several categories of patients seem reasonably clear.

Presentation with an Unexplained Systemic Embolic Event. These patients should undergo contrast TEE as part of the initial evaluation.

Asymptomatic Patient with a Hemodynamically Insignificant IAS Communication Detected During Testing for Another Clinical Condition. Given the large number of these patients, the very low embolic incidence rate, and the significant possibility of morbidity and mortality from any of the possible interventions, specific treatment is unwarranted. If the patient is to undergo general or regional anesthesia for any reason, then techniques that avoid air entrainment should be used. Attention should be paid to the prophylaxis of DVT, especially in the perioperative period. Recreational divers must be informed of their potential risk.

Patient Who Has Had a Clear Systemic Thromboembolic Event and Has a Demonstrated, Hemodynamically Insignificant, IAS Communication. Obviously, other sources of thromboembolism should be searched for. In the situation in which the lone potential source is the IAS communication, the possibility of a venous origin of the emboli (mainly large veins at or below the pelvis) should be evaluated. The presence of venous thrombus may warrant a specific treatment plan with a specific endpoint (e.g., a 6-month course of anticoagulation for DVT related to recent mechanical trauma). However, without such a source there is less assurance in recommending any specific therapy. In younger patients, in whom atheromatous embolization is unlikely, chronic anticoagulation is reasonable. In older patients, even those without demonstrable atherosclerotic disease, no general recommendations can be made. Aspirin in this group would seem as reasonable an alternative as coumadin.

Recurrent Embolization Despite Adequate Anticoagulation. Closure of the communication should be considered. Closure should also be considered after an initial systemic embolic event in children, as well as in women who wish to bear children, as anticoagulation is associated with significant risks in these patients. Surgical closure of an IAS communication requires thoracotomy and cardiopulmonary bypass, yielding considerable morbidity and an extremely low but finite mortality. Results of surgical closure are uniformly excellent. Recently, a percutaneous transcatheter method of ASD closure has been described.[76] Success rates have been high in selected patient groups and follow-up for over a year has been quite favorable. This technique holds promise as a safe alternative to open heart surgery.

SUMMARY

It is apparent that the anatomy and physiology of the IAS are key to understanding its role in systemic embolization. Any communication may give rise to right to left flow across the septum under the right circumstances. The absolute degree of the association of IAS communications with systemic thromboembolic events cannot be precisely defined. The therapeutic approach must be tailored to the clinical situation.

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DEEP VEIN THROMBOSIS

Brian S. Kaufman, MD, and Christopher C. Young, MD

Deep venous thrombosis (DVT) is a common clinical entity affecting an estimated 5 million patients each year in the United States.[143] Surgical patients are at increased risk for the development of DVT: thrombi may be present prior to surgery or may develop in the intraoperative or postoperative period. Anesthesiologists, therefore, need to be familiar with the risk factors, diagnostic measures, current management principles, and prophylaxis of DVT. Additionally, the anesthesiologist may be able to influence directly the incidence of perioperative DVT by the choice of anesthetic technique. Familiarity with this disease entity should therefore lead to optimal perioperative management of this difficult disorder.

A past history of DVT may be the single most important risk factor among the many factors that predispose the patient undergoing surgery to this condition. When patients with this history undergo surgical procedures, the frequency of postoperative thrombosis is 60% to 70%.[50] Postoperative immobilization is also associated with a high incidence of DVT, particularly in the patient sustaining an injury to the lower extremities.[29, 146] Other risk factors for perioperative DVT are outlined in Table 1.[50, 51] In the 1850s, Virchow described a triad of factors necessary to produce intravascular thrombosis: (1) venous stasis, (2) changes in the coagulation properties of the blood, and (3) intimal injury. More recently, it has been recognized that thrombi may develop in the absence of intimal injury.[143] General anesthesia is associated with decreased venous flow in the lower extremities.[120] Surgical maneuvers, such as cross-clamping of the aorta during aortic aneurysm resection, can produce further impairment of venous blood flow. Under these

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Table 1. FACTORS FACILITATING THE DEVELOPMENT OF POSTSURGICAL OR POSTTRAUMATIC DVT

History of thromboembolic disease	Use of oral contraceptives
Immobility	Obesity
Lower extremity injuries or surgery	Gram-negative sepsis
Age	Pregnancy
Heart failure	Malignancy
Varicose veins	General anesthesia

From Kaufman B: Deep vein thrombosis and pulmonary embolism in the injured patient. *In* Capan LM, Miller SM, and Turndorf H (eds): Trauma: Anesthesia and Intensive Care. Philadelphia, JB Lippincott, 1991, p 822; with permission.

conditions, activation of clotting enzymes may provide a sufficient stimulus for the development of venous thrombosis. The development of thrombi may also reflect the effects of decreased activity of endogenous inhibitors of the clotting cascade.[51] Eighty-one percent of the patients receiving elective abdominal surgery (43 of 53) evaluated by Knight and associates[112] exhibited depression of fibrinolytic activity on the first postoperative day. Of the 13 patients whose fibrinolysis was most depressed, 10 developed DVT. In addition, the median fibrinolytic activity of patients who developed DVT on the first postoperative day was significantly lower than that of the remainder of the group.[112]

Most thrombi originate as platelet clumps that develop in the region of venous valves in the lower extremities (particularly the calves).[172] Because blood flow is decreased or even stagnant in these areas, the endothelium may become hypoxic and release mediators that attract and activate platelets and leukocytes.[172] These activated cells release thrombogenic factors causing the development of a fibrin thrombus that grows by the addition of more platelets and fibrin. The thrombus may either break off and embolize, undergo lysis by the endogenous thrombolytic system, or become organized and incorporated into the wall of the vessel.[143]

Not all venous thrombi of the lower extremity pose an equal risk. Thrombi that are localized to the calf veins and that do not extend over time to more proximal veins have minimal embolic potential.[144] Excellent clinical outcomes have been reported for this patient population even without the use of anticoagulant therapy.[144] More proximal lower extremity thrombi contribute significantly to perioperative morbidity and mortality. More than 90% of all clinically significant pulmonary emboli originate from proximal lower extremity DVT, with the remainder originating from the pelvic veins, the renal veins, the upper extremity, and the right heart.[75, 89, 186]

DIAGNOSIS

Diagnosing DVT by clinical findings alone is difficult, because the signs and symptoms of this disorder can also be produced by nonthrombotic disorders.[82, 142] Most patients with postoperative DVT are either asymptomatic or have relatively minor signs and symptoms, probably because total occlusion of the lower extremity veins is unusual. Conversely, the majority of patients with signs and symptoms suggestive of lower extremity DVT do not have a clot(s) present in their leg veins.[82, 142] Therefore, therapeutic decisions made on the basis of clinical findings alone may unnecessarily place the patient at risk for the hemorrhagic complications of anticoagulant therapy.

Both invasive and noninvasive procedures can be employed to determine more accurately if DVT is present. Although these tests are costly and may be associated with complications, the overall morbidity is considerably less than that associated with inappropriate pharmacologic or surgical intervention. This is particularly true in patients at increased risk for complications of anticoagulation therapy such as trauma victims, neurosurgical patients, and the elderly.

Venography

Venography is considered the gold standard for diagnosing DVT.[82, 170] Hull and associates[90] documented the safety of withholding anticoagulant therapy in patients with clinically suspected DVT and negative venograms. Their results provide support for the notion that a normal venogram of the lower extremities excludes the diagnosis of leg DVT. Lower extremity venography is accomplished by injection of a radiocontrast medium into a dorsal pedal vein. The entire deep venous system of the leg should be visualized, including the calf, popliteal, femoral, and iliac veins. The accuracy of this test is dependent on the quality of the study and the skill of the interpreter.[88] The most reliable criterion for diagnosing thrombosis is the presence of a constant intraluminal filling defect on sequential films. Complications of this invasive procedure include local pain at the site of dye injection, allergic reactions, and superficial or deep venous thrombophlebitis secondary to irritation by the contrast medium.[21]

Noninvasive Diagnostic Procedures

Noninvasive tests are useful for diagnosing DVT and can eliminate the need for venography in most patients. The advantages of using noninvasive tests initially include less patient discomfort, minimal morbidity, and portability of the diagnostic equipment. Four such methods have received extensive clinical trials: the ^{125}I-fibrinogen uptake test, impedance plethysmography, Doppler ultrasonography, and B-mode ultrasonography with or without a simultaneous Doppler flow study.

^{125}I-Fibrinogen Uptake Test

The ^{125}I-fibrinogen uptake test has been extensively used for clinical research to evaluate the incidence of postoperative DVT. Intravenously injected ^{125}I-labeled fibrinogen is incorporated into fresh thrombus and the resulting increase in surface radioactivity is detected with a gamma scanner.[93] The patient can be repeatedly scanned for up to 5 to 7 days following a single intravenous injection of the tracer. The fibrinogen uptake test reliably detects fresh calf vein thrombi. Because the vast majority of postoperative DVT begin in calf veins, this test has proven to be useful for evaluating the efficacy of various prophylactic measures employed to decrease the incidence of DVT. The fibrinogen uptake test detects over 90% of acute calf vein thrombi but only 60% to 80% of more proximal thrombi.[82, 93] In addition, it is not reliable for detecting thrombi in the pelvis and upper thigh, because these veins are in close proximity to the bladder, which accumulates radioactive urine. Therefore, fibrinogen scanning should never be used as the only diagnostic test for DVT. The clinical significance of a positive fibrinogen scan has been questioned, because only a small proportion of calf vein thrombi extend to more proximal veins from which the embolic risk is greater.

Impedance Plethysmography

Impedance plethysmography utilizes an externally applied electrical current to assess changes in leg impedance, which increases when the volume of blood within the leg is decreased and decreases with increased blood volume. This test utilizes deliberate changes in leg blood volume produced by rapid inflation and deflation of a pneumatic cuff applied around the mid thigh. The normal curve has a rapid rise and fall. If significant venous obstruction is present, the deflation curve is prolonged and flattened (Fig. 1). Each vascular laboratory establishes norms for the rates of rise and fall of leg impedance in response to cuff inflation and deflation. This technique is highly sensitive and specific for detecting thrombi that cause obstruction of the popliteal, femoral, and iliac veins, but it is less sensitive for detecting occlusion of calf veins, because thrombi in these veins do not produce significant outflow obstruction.[88, 93] Small nonocclusive proximal vein thrombi or occlusive proximal vein thrombosis associated with well-developed collaterals may also produce false-negative results.[82] Furthermore, this test cannot distinguish between thrombotic and nonthrombotic obstruction to venous outflow. Factors like inadequate patient relaxation, reduced arterial inflow, reduced venous outflow secondary to increased central venous pressure, and extravascular compression also produce false-positive results. In patients at high risk for developing DVT, serial normal impedance tests are strong evidence against the presence of clinically significant lower extremity DVT.[86]

Combined Impedance Plethysmography and ^{125}I-Fibrinogen Scanning. If the combination of impedance plethysmography and ^{125}I-fibrinogen scanning yields negative results in patients with clinically suspected DVT, the predictive value is as good as that of a negative venogram.[82, 91] However, Paiement and colleagues[161] evaluated 537 patients undergoing total hip replacement and found that the combi-

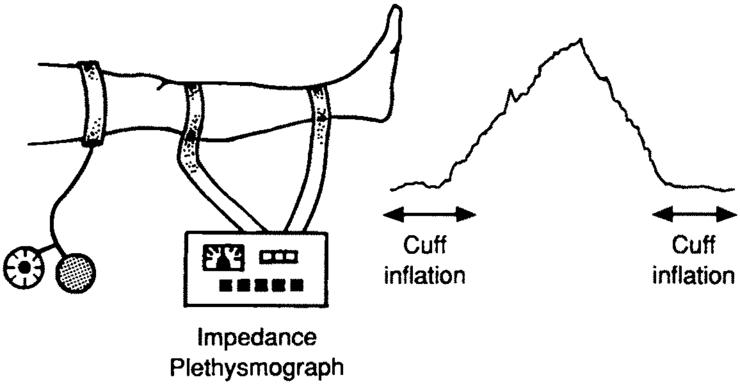

Figure 1. Impedance plethysmography. *Left,* schematic drawing of the system showing the pressure cuff applied to the midthigh and the sensing electrodes connected to the impedance plethysmograph. Two additional electrodes not shown deliver small electrical currents to the leg. Cuff inflation and deflation produce changes in the volume of the veins of the calf muscles, altering the impedance of the leg to externally delivered electrical current and causing upward and downward deflection of the impedance curve (*right*). In the presence of venous obstruction, the rate of venous filling and emptying is reduced, causing a decrease in the rates of the rise and decline of the impedance curve. (*From* Kaufman B: Deep vein thrombosis and pulmonary embolism in the injured patient. *In* Capan LM, Miller SM, Turndorf H (eds): Trauma: Anesthesia and Intensive Care. Philadelphia, J B Lippincott, 1991, p 823; with permission.)

nation of ^{125}I-fibrinogen scanning and impedance phlebography resulted in a sensitivity of only 23.2% for detecting thigh thrombi and an overall sensitivity for DVT of 47.1%.[161] Similarly, Hull et al[92] reported a sensitivity for detecting proximal vein thrombi of 48% with the use of these two tests in a similar patient population. Thus, these tests seem to be of no value in screening for DVT in patients requiring hip arthroplasty.

Doppler Ultrasonography

Doppler ultrasonography is another sensitive test recommended for the detection of proximal DVT, but like impedance plethysmography, it is not reliable for the diagnosis of calf vein thrombosis.[82, 93, 192, 201] The test is based on the transcutaneous detection of venous flow patterns. The examination is performed by placing a probe over the underlying vein. After the characteristic sound of venous flow is detected, the extremity is compressed distally. This maneuver normally produces an acceleration of blood flow and an augmentation of the venous sound. In the presence of occlusive proximal DVT, this augmentation is absent or diminished. The examination is inexpensive and the device is more portable than the impedance plethysmograph. However, because interpretation of the results is subjective, the sensitivity and specificity of the test depend upon the skill and experience of the investigator.[93]

B-Mode Ultrasonography

Real-time B-mode ultrasonography has recently been used for diagnosing DVT of the lower extremities and is rapidly becoming the noninvasive procedure of choice for initial evaluation of patients suspected of having acute DVT.[45] The procedure is simple, requires minimal patient cooperation, has no documented side effects, and can usually be completed by experienced personnel within 15 minutes.[15] Longitudinal and cross-sectional views of the leg can reveal clots in the iliofemoral, popliteal, and calf veins. Several studies have demonstrated that real-time imaging is more sensitive and specific than methods such as impedance plethysmography that rely only on hemodynamic changes.[45, 65]

Blood flow through the imaged veins can be evaluated simultaneously by audible Doppler ultrasound. The combination is termed *duplex scanning*. Real-time B-mode ultrasonography with or without Doppler ultrasound is capable of detecting the nonocclusive and infrapopliteal thrombi that are often missed by hemodynamic techniques.[45] Diagnostic criteria for DVT with real-time B-mode ultrasonography include (1) noncompressibility of the vein underlying the probe when gentle pressure is applied, (2) detection of intraluminal echogenic material,

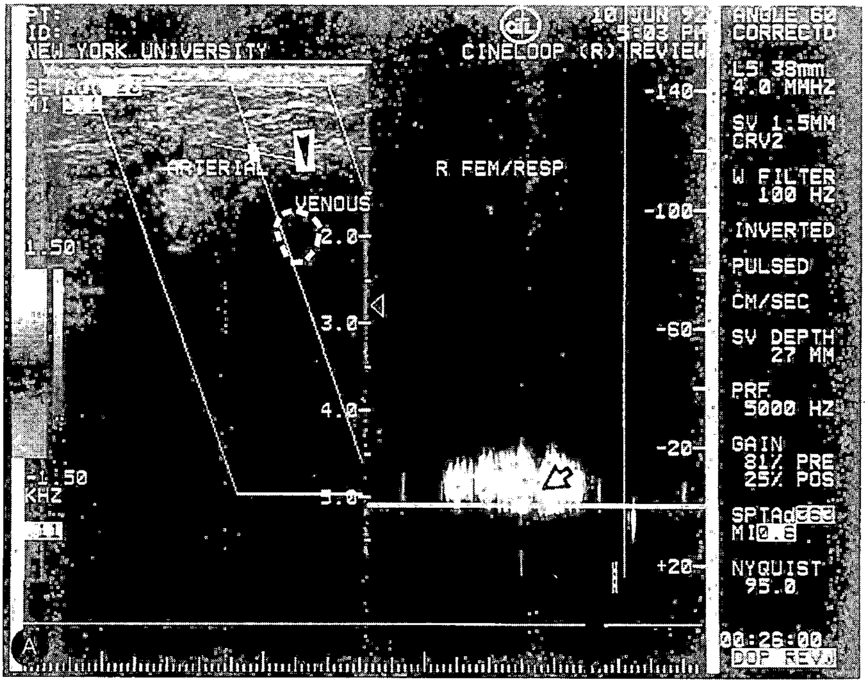

Figure 2. *A*, Normal venous duplex scan. The venous Doppler signal is present and is augmented during inspiration *(arrow)*. The femoral vein outlined by dots is widely patent *(arrowhead)*.

Illustration continued on opposite page

and (3) loss of venodilation during the Valsalva maneuver. With duplex imaging, the diagnostic criteria include (1) absent intraluminal signal, (2) absence of respiratory variation, and (3) reduced or absent response to leg compression (Fig. 2).

The reported accuracy of real-time B-mode ultrasonography and duplex scanning varies depending on the population studied, the criteria used for a positive diagnosis, and the technique used to evaluate the leg veins.[27, 110, 114] Several studies report a sensitivity and specificity of 86% to 100% for the detection of proximal DVT.[8, 72, 118, 167] Isolated calf vein thrombosis is more difficult to detect.[27] Serial scans can be used to follow high-risk patients in order to detect thrombosis extending to more proximal veins. Recent advances that encode Doppler signals as colors superimposed on the B-mode image may increase the sensitivity of duplex scanning for detecting clots in this location.[15, 167]

The cost and complications of the various invasive and noninvasive methods used for the diagnosis of DVT limit their usefulness as screening tests. The need for a highly sensitive and inexpensive test with rapid availability of results has led to the development of another method: testing the blood for the presence of clot degradation products.[175] Plasmin digestion of cross-linked fibrin results in the release of several fibrin fragments into the blood stream. D-Dimer is one such

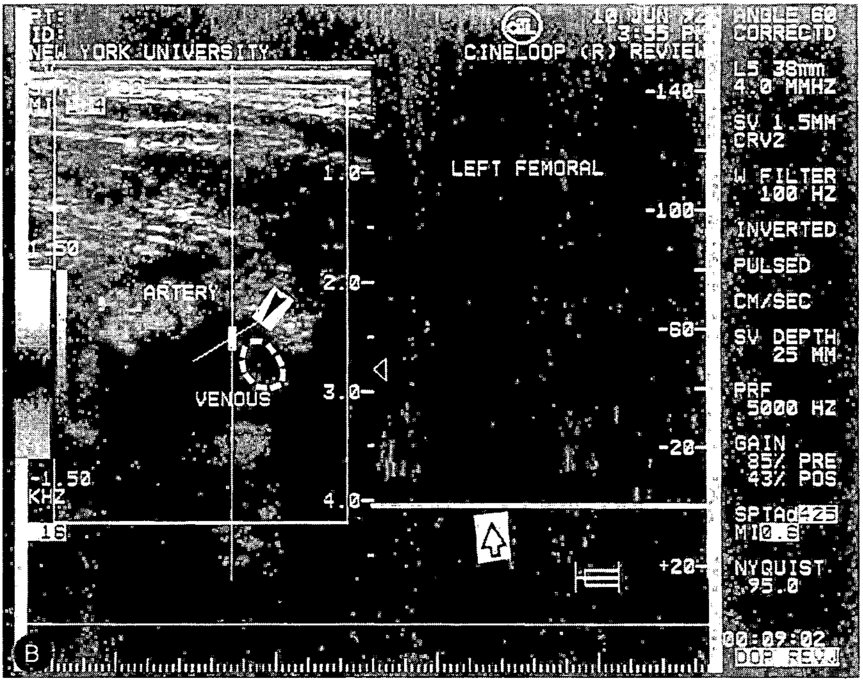

Figure 2 *(Continued). B,* Abnormal venous duplex scan. The venous Doppler signal is absent *(arrow).* The vein outlined by dots is noncompressible *(arrowhead).*

product; its level can be measured by immunoassay using monoclonal antibodies.[175] Several recent studies have documented that a normal value excludes the diagnosis of DVT (sensitivity = 100%), whereas an increased level supports the diagnosis.[28, 157, 175] Unfortunately there are many clinical conditions that can produce an increased D-dimer level, limiting the specificity of the test.[28, 157, 175] Therefore, the presence of an elevated D-dimer level is insufficient evidence for initiating anticoagulant therapy in patients with suspected DVT. If further clinical research substantiates the reliability of normal values in excluding DVT, a reasonable diagnostic approach might be an initial measurement of the D-dimer level, with further invasive or noninvasive evaluation only in those patients with an elevated value.[28]

PREVENTION

The fact that pulmonary thromboembolism is not a disease in itself but rather a complication of DVT leads to the conclusion that if perioperative DVT can be avoided, pulmonary embolism (PE) will be prevented as well.[143] Prophylaxis or early treatment of DVT may also decrease the long-term incidence of the postphlebitic syndrome (chronic pedal edema, pain, and stasis changes in the skin). This may benefit more patients than the prevention of PE. Many measures have been utilized to decrease the incidence of DVT. These interventions can be divided into two categories: (1) those decreasing coagulability of the blood, and (2) those decreasing venous stasis in the leg veins. Because thrombi begin to develop before or during surgery in the majority of patients, prophylactic measures should be initiated preoperatively or intraoperatively.

PHARMACOLOGIC PROPHYLAXIS

Heparin Anticoagulation

Low-dose heparin anticoagulation is the most widely used prophylactic measure in surgical patients. Many studies have demonstrated the efficacy of a 5000-U dose of heparin administered subcutaneously every 8 to 12 hours.[14, 100, 101, 149, 150, 169, 202] In patients undergoing elective surgery, therapy is usually initiated 2 hours before surgery and continued for 7 days postoperatively or until the patient is ambulatory.[100]

Low-dose heparin augments the activity of antithrombin III, a potent inhibitor of activated factor X (Xa) and thrombin, resulting in interruption of both the intrinsic and extrinsic clotting pathways. There are only minimal changes in conventional clotting tests such as the activated partial thromboplastin time (APTT). An increased frequency of perioperative bleeding has been reported when heparin is given every 8 hours.[109] Administration of heparin every 12 hours is therefore recommended for DVT prophylaxis in surgical patients.[14, 109]

Most authors believe that low-dose heparin prophylaxis is safe, effective, and well tolerated.[100, 169] When patients receive 5000 U every 12 hours in the perioperative period, there is only a small risk of increased bleeding. The increase in wound hemorrhage is almost invariably minor if the patient is hemostatically competent and has not taken aspirin for 5 days prior to surgery. Monitoring of clotting parameters is not required in these patients. However, Pachter and Riles[159] reported a 27% incidence of bleeding complications (wound hematoma 23%, gross hematuria 4%) in patients undergoing general surgery who were receiving DVT prophylaxis at this dosage level. The incidence of these complications in patients not treated with heparin was only 1.4% in this study. The authors suggest that low-dose heparin should be reserved for patients who are older than 40 years and have additional risk factors for the development of DVT. Van Ooijen[210] reported a wound hematoma incidence of 32% in patients receiving 5000 U of heparin every 12 hours compared with 15% in a control group. However, significant hematomas resulting in wound dehiscence did not occur in any of these patients. Concerns regarding the hemorrhagic complications of low-dose heparinization led Negus and associates[147] to evaluate the effects of ultra–low-dose intravenous heparin therapy. Patients received 1 IU/kg of heparin intravenously for 3 to 5 days during and after surgery and were compared with patients who were receiving placebo. Four percent of the heparin group had thrombotic complications, whereas the incidence was 22% in the control group.

The controversy about the safety of low-dose heparin helps explain the reluctance of surgeons to use it when there is an increased risk of hemorrhagic complications, such as in trauma patients or in those undergoing vascular procedures.[150] A definite reduction in mortality must be demonstrated before this method of prophylaxis is widely accepted. Unfortunately, despite a decrease in the incidence of DVT, no clinical trials to date have demonstrated the efficacy of prophylactic heparin therapy in reducing mortality.[100, 101, 159, 169] The only indirect evidence for the efficacy of heparin prophylaxis is a reduced frequency of PE at autopsy.[169] The failure to demonstrate a decrease in mortality in clinical trials may result from limitations of the studies rather than to a lack of effect. To demonstrate a significant reduction in mortality rate, a series of thousands of patients would be necessary, as the clinical end point (fatal PE) is an uncommon event. The small number of patients in the studies attempting to evaluate the efficacy of low-dose heparin would therefore be insufficient to demonstrate a reduced mortality from PE even if death indeed was decreased. A 1988 review surveyed the results of all the published randomized trials of perioperative prophylaxis with subcutaneous heparin.[44] Over 70 trials involving more than 16,000 patients were reviewed. The incidence of DVT diagnosed by fibrinogen scans was reduced approximately 67%, proximal DVT by 56%, and fatal PE by 64%. There was no apparent increase in deaths ascribed to causes other than PE. A substantial increase in serious bleeding was not found. Whether the results of this meta-analysis will influence the practice of surgeons who remain reluctant to use low-dose heparin for DVT prophylaxis is uncertain.

Low-dose heparin may be less effective in the setting of lower extremity surgery than in general surgical patients. Williams and associates[214] could not demonstrate a protective effect of this method in patients undergoing hip surgery or amputations of the leg. Hampson et al[74] also noted that low-dose heparin failed to prevent DVT following hip replacement. The decreased efficacy of low-dose heparin in these situations may be secondary to factors present only in orthopedic patients. For example, during hip replacement, intermittent compression of the common femoral vein by manipulation of the leg can produce venous stasis, endothelial damage, and release of tissue thromboplastin, counteracting the anticoagulant effect of fixed low doses of heparin. Leyvraz and associates[121] demonstrated that heparin prophylaxis was effective in patients undergoing total hip replacement if the dose of the drug was adjusted to keep the APTT between 31.5 and 36 seconds. This approach achieved DVT protection without a significant increase in hemorrhagic complications.

Low-dose heparin prophylaxis may also be less effective in trauma victims. Increased concentrations of thromboplastin may be present in the serum of traumatized patients because of tissue injury.[4, 5, 96] DVT may thus begin to develop prior to the initiation of prophylaxis. Under these circumstances, low-dose heparin may not be effective, as the coagulation cascade would have already been set in motion. The scarcity of data demonstrating the efficacy of heparin prophylaxis in trauma patients, combined with the likely increased risk of hemorrhagic complications, precludes the routine use of low-dose heparin in this group of patients. Fear of bleeding has also limited the use of heparin (and other methods utilizing anticoagulants) for DVT prophylaxis in patients undergoing neurosurgical procedures.

The combination of dihydroergotamine (DHE) and low-dose heparin as a prophylaxis for postoperative DVT may be more effective than low-dose heparin alone and may be associated with a decreased rate and intensity of hemorrhagic complications. DHE is a vasoconstrictor that predominantly affects the capacitance vessels; it has a minimal effect on resistance vessels. Phlebograms obtained before and after administration of 0.5 mg of DHE demonstrated a significant reduction in the diameter of the tibial, soleal, and femoral veins.[106] DHE allegedly counteracts venous stasis and accelerates venous return from the lower extremities.[81, 145] It may also work through effects on antithrombin III and by inhibiting platelet aggregation.[106] A multicenter trial has compared DHE (0.5 mg) plus heparin (5000 IU or 2500 IU) injected subcutaneously every 12 hours for 5 to 7 days to 5000 IU subcutaneous heparin given at similar intervals.[145] It was theorized that if venous stasis could be reduced by the increased venous tone produced by the DHE, less heparin would be necessary to prevent thrombus formation. The combination of DHE with 2500 IU of heparin was as effective as standard low-dose heparin in preventing DVT; the incidence of bleeding complications was also similar. However, the DHE and 5000 IU heparin combination provided greater prophylaxis against DVT than did low-dose heparin alone. Excessive postoperative bleeding or wound hematoma occurred no more frequently in the group receiving the DHE and 5000 IU heparin combination than in the standard low-dose heparin group. However, one patient developed bowel necrosis possibly related to the use of DHE. This combination was also compared with low-dose heparin in a study of patients undergoing major abdominal surgery or elective hip replacement.[105] DHE combined with 2500 IU heparin was as effective as standard low-dose heparin in major abdominal surgery, and DHE combined with 5000 IU was significantly more effective than 5000 IU heparin given subcutaneously preoperatively and then every 8 hours postoperatively. Despite the favorable results reported in a multicenter trial, this therapeutic combination is not widely used.[32] Potential exacerbation of hypertension and cardiac and arterial occlusive diseases with the use of an ergot derivative is the primary concern that limits the use of this prophylactic regimen.[32]

Studies indicate that despite the documented effectiveness of low-dose heparin in reducing the incidence of DVT, many surgeons avoid this agent because of fear of hemorrhagic complications.[47, 160] Orthopedic surgeons, in particular, have been reluctant to use heparin or oral anticoagulants in joint replacement procedures, as bleeding into the joint may lead to failure of the surgery.[160]

Heparin is not a homogeneous substance; it is a mixture of polysaccharide molecules that vary in molecular weight from 2000 to 40,000 d.[178] It has been demonstrated in animals that low molecular weight fractions of heparin are as effective as standard heparin in preventing venous thrombosis but produce less bleeding.[178] A part of the reason for this effect is that the smaller the heparin molecule, the less it inhibits platelet function.[178] Low molecular weight heparins (LMWH) are currently being evaluated as agents for DVT prophylaxis in humans. Interest in LMWH was stimulated by the observation that low molecular weight fractions of standard heparin maintain their ability to inhibit factor Xa while losing their ability to prolong the APTT; less bleeding is noted in experimental models with the use of LMWH at an equivalent antithrombotic effect.[83]

The major anticoagulant effect of heparin results from an interaction of heparin with antithrombin III, which markedly increases the ability of the enzyme to inactivate clotting.[83] Standard heparin simultaneously binds thrombin and accelerates its catalysis, resulting in prolongation of the APTT and increased risk of bleeding. LMWH fractions are unable to interact with antithrombin III and thrombin at the same time; this difference in binding characteristics is responsible for the different activities of unfractionated heparin and LMWH.[83] LMWH therefore may have a limited anticoagulant effect, whereas maintaining its antithrombotic activity.

Several randomized studies have been published documenting that LMWH is at least as safe and effective as unfractionated heparin in patients undergoing major abdominal surgery.[83] For example, Kakkar and associates[104] compared 5000 IU of unfractionated heparin to LMWH with therapy started preoperatively. The incidence of DVT was significantly lower in the LMWH group, whereas the incidence of excessive postoperative blood loss and wound hematoma was similar in both groups.

The effectiveness of LMWH for preventing DVT following elective hip surgery was clearly documented by Turpie and colleagues.[208] Even though prophylaxis was begun 12 to 24 hours after surgery, the incidence of DVT documented by venography was only 12% compared to 42% in the untreated control group. Levine et al[119] compared LMWH with unfractionated heparin beginning 12 to 24 hours following elective hip surgery. There was no significant difference in the incidence of DVT between the two groups, but there was a significantly lower incidence of hemorrhagic complications in patients receiving LMWH.

When prophylaxis was initiated prior to elective hip replacement, Planes et al[164, 165] documented a significantly lower incidence of DVT in a LMWH group compared to patients receiving 5000 IU unfractionated heparin every 8 hours (12.5% vs 25%). Total blood transfusion requirement was significantly higher in the unfractionated heparin group.

The efficacy of LMWH in preventing postoperative DVT after total hip replacement has also been compared to dextran 70.[54] Patients in the LMWH group received a daily subcutaneous injection of 40.6 mg of enoxaparin, which was initiated 12 hours preoperatively and then continued for 7 days. Patients in the dextran 70 group received 500 mL intravenously during surgery, a second dose 4 to 6 hours later, and then third and fourth doses on days 1 and 3 after operation. The incidence of DVT documented by venogram was significantly lower in the LMWH group (6.5% vs 21.6%).[54] Postoperative blood loss and number of postoperative blood transfusions were also significantly less in the LMWH group.

The results of these trials provide evidence that LMWH can prevent DVT in high-risk surgical patients, may be more effective than standard low-dose heparin or dextran 70 in orthopedic surgery, and may be associated with a decreased risk of hemorrhagic complications. Additional potential benefits include its once-a-day dosage requirement and the lack of need for laboratory tests. LMWH is commercially available in Europe but not in the United States at this time.

Coumarin Anticoagulation

Coumarin derivatives (dicoumarin, warfarin) also have been used for prophylaxis against DVT.[140, 185] Sevitt and Gallagher[185] studied the efficacy of full anticoagulant doses of phenindione (a warfarin-like drug) in 300 patients with femoral neck fractures. Only 2.7% of the phenindione-treated patients had clinical evidence of DVT as opposed to 29% of the untreated controls. Although minor hemorrhagic complications occurred more frequently in the treated group, the authors did not find an increased incidence of wound bleeding or an increased need for blood transfusion.[169, 185] Similar results have been reported with the use of warfarin and dicoumarol in patients with femoral neck fractures.[26, 140]

Full anticoagulation prior to surgery has very limited acceptance. In an attempt to limit concerns about intraoperative and postoperative bleeding, a two-step regimen has been suggested.[60] Small doses of warfarin are administered before surgery to prolong the prothrombin time (PT) by 1.5 to 3.0 seconds over control. Doses of this magnitude provide some protection against DVT without increasing the risk of intraoperative bleeding. Postoperatively, the dose of warfarin is increased to prolong the PT to 1.5 times control.[60] This method cannot be used in patients requiring emergent surgery, because it takes several days for warfarin to take effect.

Dextran

Dextrans with average molecular weights of 40,000 (dextran 40) and 70,000 (dextran 70) possess significant antithrombotic properties as a result of (1) reduced platelet aggregation, (2) change in fibrin structure, (3) change in mechanical properties of the fibrin clot, (4) facilitated fibrinolysis, and (5) increased blood flow due to improved rheology.[69] Because of these effects, there has been concern that using dextrans for DVT prophylaxis may increase the risk of bleeding.

Both dextran 40 and dextran 70 are at least as effective as low-dose heparin in preventing DVT in orthopedic patients.[69, 70] However, this form of therapy is less effective than low-dose heparin prophylaxis in patients undergoing nonorthopedic surgery.[69] The usual dose of dextran is 500 to 1000 mL every day or every other day for 2 to 3 days or until the patient is ambulatory. Both dextran 40 and dextran 70 are potent volume expanders. Careful monitoring of central venous pressure or pulmonary artery wedge pressure is recommended to minimize the risk of iatrogenic pulmonary edema. Minor or major allergic reactions occur in approximately 1% of patients receiving dextrans.[70] Anaphylactoid reactions occur with incidences of 0.013% and 0.025% following the administration of dextrans 40 and 70, respectively.[124] Preexisting dextran-reactive antibodies have a role in producing anaphylactoid reactions. The risk of these uncommon complications has been markedly reduced, although not eliminated, since the introduction of hapten inhibition.[19, 131] A monovalent hapten-dextran preparation (dextran 1) with an average molecular weight of 1000 combines with dextran-reactive antibodies without producing an anaphylactoid reaction when infused a few minutes before dextran 40 or 70 is started. These antibodies will thus not be available to react with subsequently infused dextran.

Dextran fractions with molecular weights of less than 50,000 d traverse the glomeruli. They are not reabsorbed but are retained in the renal tubules as water is removed. The remaining highly viscous filtrate may cause an increase in tubular back pressure, predisposing the patient to renal failure.[37] The possibility of this complication has blunted the enthusiasm for using dextrans for DVT prophylaxis, although this problem is quite rare (less than 1 in 140,000).[13, 195]

Before the initiation of any form of anticoagulant prophylaxis, certain laboratory tests should be performed. These include (1) a coagulation profile consisting of at least the PT, APTT, and platelet count; (2) measurement of hematocrit; and (3) urine and stool examination for the presence of occult blood. If these tests are normal and the patient is not bleeding actively and is not having surgery at a site where increased bleeding may be dangerous (e.g., neurosurgery), anticoagulants can be used for DVT prophylaxis with a reasonable degree of safety. Close monitoring for evidence of excessive anticoagulation, heparin-induced thrombocytopenia, and occult bleeding is essential after starting anticoagulation. The APTT and platelet count should be monitored if the patient is on heparin, whereas the PT should be monitored if warfarin derivatives are being used.

MECHANICAL METHODS OF PREVENTING DEEP VEIN THROMBOSIS

The mechanical techniques most frequently utilized to prevent perioperative DVT include early mobilization, leg elevation, individually fitted elastic stockings, and intermittent pneumatic compression. These techniques attempt to prevent venous stasis, which is the major predisposing factor in the development of DVT. Early ambulation may be a useful method for preventing DVT, although it has not been rigorously evaluated in controlled trials. The benefits of early ambulation are probably related in large part to the restoration of flow in the lower extremity veins following a period of immobilization.[117] Leg elevation and standard elastic stockings are without benefit in the prevention of DVT.[31, 173] However, individually fitted elastic stockings increase the velocity of venous blood flow in the legs, pelvic veins, and inferior vena cava by producing a pressure differential between the ankles and the knees.[184, 217] The use of these stockings significantly decreases the incidence of DVT following abdominal surgery.[184] In addition, the combination of graduated elastic compression stockings with either low-dose heparin or intermittent sequential pneumatic compression results in a significantly lower incidence of DVT following major abdominal surgery than when low-dose heparin or pneumatic leg compression is used alone.[183, 217] Calf muscle exercises, either in the form of pedals strapped to the patient's feet or by application of intermittent pneumatic compression to the calf, have been demonstrated to be as effective as anticoagulant treatment in DVT prevention.[52] Intermittent pneumatic compression appears to be the most comfortable method and has been studied most extensively (Fig. 3).

In many clinical trials, perioperative application of pneumatic leg compression reduced the incidence of postoperative DVT.[3, 52, 79, 111] In three controlled studies in which legs were scanned with the ^{125}I-fibrinogen test for 1 week, this technique reduced the incidence of DVT by 60% to 82%.[79, 151] Pneumatic leg compression prevents venous stasis; peak femoral venous blood flow may increase by 240% during this maneuver.[151, 179] Devices that sequentially compress the calf and thigh produce higher femoral blood flow velocities than single-chamber units.[151] However, despite this improvement in hemodynamics and an enhanced fibrinolytic activity, a greater antithrombotic effectiveness of the more expensive sequential compression device has not been clearly demonstrated.[181] The decreased incidence of DVT following the use of pneumatic leg compression may result from other factors in addition to the prevention of venous stasis.[79] Intermittent pneumatic compression not only empties the leg veins but also causes venous occlusion.[3] Both venous occlusion and direct compression result in the release of plasminogen activators (found in high concentrations in all layers of the vein wall) into the blood stream, preventing the expected postoperative decrease in fibrinolytic activity.[3, 38, 181] Indeed, fibrinolytic activity may remain high for more than 18 hours after discontinuation of compression.[52] Intraoperative compression of the arm veins can also prevent DVT and the postoperative decrease in blood fibrinolytic activity. Knight and Dawson[111] demonstrated a 50% reduction in the incidence of DVT in patients receiving intermittent pneumatic arm compression. However, Hills and associates[79] showed that this method had no effect on the incidence of DVT in patients with cancer undergo-

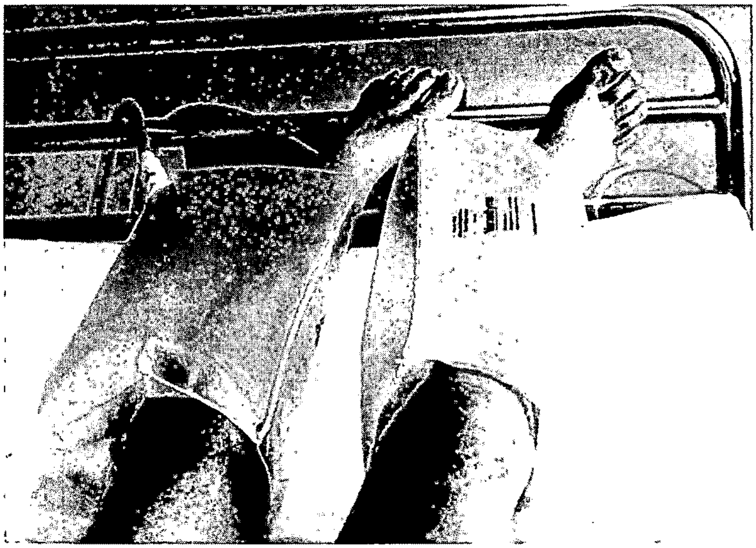

Figure 3. Pneumatic compression boots applied to the legs of a patient for deep vein thrombosis prophylaxis.

ing surgery. The lack of efficacy in this group of patients may be related to the fact that leg compression also did not prevent the postoperative decrease in blood fibrinolytic activity. The failure of pneumatic compression to prevent DVT in patients with carcinoma supports the contention that it is the release of plasminogen activators that produces the beneficial effects of this therapy. The most pronounced increase in fibrinolytic activity resulting from limb compression occurs locally rather than systemically; the amount of fibrinolytic substances released is related to the mass of the compressed tissue.[204] Therefore, pneumatic compression of the leg produces the most profound increase in fibrinolytic activity in the blood contained in the lower extremity, which is often a fertile area for development of DVT. Pneumatic leg compression also increases the local generation of prostacyclin, which may directly stimulate plasminogen activator, leading to hydrolysis of fibrin and inhibition of platelet aggregation.[71]

Leg compression should be applied at the earliest opportunity. It may be started in the operating room prior to induction of anesthesia.[204] If the patient is hospitalized before surgery, the treatment should be applied upon patient immobilization and continued throughout the operative and postoperative periods until the patient is ambulatory. Mechanical techniques such as pneumatic leg compression are particularly attractive for trauma victims or patients undergoing neurosurgical procedures in whom the risk of anticoagulant therapy is increased.

ASSESSMENT OF RISK FACTORS

Several factors should be considered during the selection of a prophylactic measure: (1) Is the patient at significant risk for developing thromboembolic complications? (2) Does the patient have a coagulopathy? (3) Does the site or nature of the surgical procedure preclude the use of a specific technique?

Surgical patients are commonly classified as low, moderate, or high risk for perioperative thromboembolic complications based on the type and number of risk factors present. Low-risk patients are (1) those younger than 40 years without any additional risk factors for DVT having uncomplicated elective abdominal or thoracic procedures, and (2) those older than 40 years having minor elective abdominal or thoracic surgery or other minor surgical procedures requiring less than 30 minutes of general anesthesia.[130, 143] Without the use of prophylactic measures, these patients have a risk of less than 10% for developing DVT in the calf veins and a risk of less than 1% for developing proximal DVT.[130, 143]

Moderate-risk patients are those younger than 40 having surgical procedures under general anesthesia that are expected to last more than 30 minutes and those who have one or more additional risk factors for developing DVT. These patients have a 10% to 40% risk of developing calf thrombi and a 2% to 10% risk of developing proximal DVT.[130]

High-risk patients include (1) those undergoing major elective orthopedic procedures on the hip or knee, especially if they have a prior history of DVT or PE; (2) those older than 40 years undergoing major abdominal surgery for malignant disease and expected to require general anesthesia for more than 30 minutes; and (3) those with traumatic injuries to the pelvis or hip. These patients have a 40% to 80% risk of developing calf vein thrombosis and a 10% to 20% risk of developing proximal DVT.[130]

There is some controversy about how the low-risk patient should be managed. Russell[177] suggests that routine prophylaxis is unnecessary in this group, as the risk of treatment outweighs the benefit. Moser[143] suggests that a single prophylactic modality should be utilized, with external pneumatic compression being the simplest to employ. The use of gradient compression stockings and early ambulation is another option for the low-risk patient.

The moderate-risk patient should receive one prophylactic modality; the most common choices are low-dose heparin or external pneumatic compression.[143] High-risk patients benefit most from the use of a combination of a pneumatic compressive device and either low-dose heparin or warfarin. It is important to remember that this combination cannot be used in all high-risk patients. There are, as we have described above, special issues in certain patient populations that limit the use of various measures either because the risks of complications are excessive or the effectiveness of a particular prophylaxis has not been established.

When effective prophylaxis cannot be used in a high-risk patient, the patient must be closely monitored for the development of proximal leg DVT. If this complication occurs and the patient still cannot be anticoagulated, an inferior vena caval filter should be placed. If a patient in this category cannot be adequately monitored for the development of proximal DVT and cannot receive effective prophylaxis (e.g., recent pelvic or hip trauma with casts in place), placement of an inferior vena caval filter should be considered.[107]

Some of the special issues involved in the use of prophylaxis in different surgical populations are discussed below.

General Surgery

The average incidence of DVT documented by fibrinogen scanning in the general surgical patient who is older than the age of 40 and has not received any form of prophylaxis is 25%.[156] Proximal DVT occurs in 7%, clinically significant PE in 1.6%, and fatal PE in less than 1%.[156]

Low-dose heparin (usually initiated 2 hours preoperatively and administered every 8 or 12 hours postoperatively) is a very effective preventive treatment. A prospective randomized multicenter study evaluated more than 4000 patients and documented a significant decrease in the incidence of DVT and fatal PE, although not in overall mortality, in patients receiving this form of prophylaxis.[169] In the meta-analysis of all the available prospective randomized clinical trials of low-dose heparin prophylaxis reported by Collins and associates,[44] the incidence of distal leg DVT diagnosed by fibrinogen scanning in patients undergoing general surgery was decreased by 67% and of proximal DVT by 56%. Most importantly, the incidence of fatal PE was decreased from 0.7% to 0.2% in the prophylactic treatment group.[44]

Although less evidence is available about the benefits of external pneumatic compression and the combination of dihydroergotamine with heparin in general surgical patients undergoing general surgery, an efficacy comparable with that of low-dose heparin in preventing proximal DVT and PE has been reported.[130, 156] Dextrans 70 and 40 may be less effective in decreasing the incidence of DVT but is as effective as the above treatments for preventing PE.[156]

The National Institutes of Health (NIH) Consensus Conference recommends routine prophylaxis of all patients undergoing general surgery at moderate or high risk as defined earlier in this article.[156] The need for prophylaxis in low-risk patients undergoing general surgery is unclear.

Neurosurgery

Prospective studies utilizing radiolabeled fibrinogen scanning have documented that 29% to 43% of neurosurgical patients develop DVT in the early postoperative period.[97, 209] The risk of this complication is the same after both spinal and intracranial operations and seems to be directly related to the length of the procedure: Valladares and associates[219] reported a twofold increase in risk following procedures that lasted longer than 4 hours.

The NIH Consensus Conference on the Prevention of Venous Thrombosis and Pulmonary Embolism recommends the use of external pneumatic compression for patients undergoing craniotomy for tumor, subarachnoid hemorrhage, arteriovenous malformation, aneurysm, arterial bypass, shunting procedures, and other intracranial problems.[156] This recommendation is based on the results of prospective randomized and controlled studies that have documented the efficacy of this technique in decreasing the incidence of DVT in neurosurgical patients. Skillman and associates[196] reported a 25% incidence of DVT documented by fibrinogen scanning and confirmed by venography in a control group of neurosurgical patients compared to an 8.5% incidence in patients in whom pneumatic compression was initiated after induction of anesthesia. Turpie et al[207] found DVT by fibrinogen scanning in 18.4% of control patients and 1.9% of patients receiving pneumatic compression postoperatively following craniotomy. Black et al[22] reported an 18% incidence of DVT documented by venography in a series of patients with subarachnoid hemorrhage secondary to ruptured intracranial aneurysm who did not receive any treatment to prevennt DVT. In contrast, only 6% of such patients developed DVT when pneumatic calf compression was started within 24 hours of hospital admission.

Limited clinical data are available about the safety of low-dose heparin in neurosurgical patients. Barnett and associates[9] evaluated 5000 IU of subcutaneous heparin begun preoperatively and continued twice daily for at least 3 days in a series of 150 patients undergoing a variety of neurosurgical procedures. No major neurosurgical complications occurred, although four wound seromas, two wound hematomas, and one nonfatal PE were reported. The efficacy of low-dose heparin for preventing DVT in neurosurgical patients was also evaluated by Cerrato and colleagues.[36] One hundred patients were randomized to a control group or to a group that received 5000 IU of heparin preoperatively and then every 8 hours for at least 7 days thereafter. The incidence of DVT detected by fibrinogen scanning was 34% in the control group compared with 6% in the low-dose heparin group.

A direct comparison of the efficacy of pneumatic compression to low-dose heparin in this patient population has not been published. Pneumatic compression must be considered to be the prophylactic method of choice at this time, because it has been demonstrated to be both safe and effective in neurosurgical patients and because even a small amount of intracranial bleeding resulting from low-dose heparin may be disastrous.

The NIH Consensus Conference recommends the use of pneumatic compression and low-dose heparin for patients undergoing extracranial neurosurgical procedures such as elective spinal cord surgery and laminectomy.[156]

If a neurosurgical patient develops DVT postoperatively, there are no data available to guide the clinician as to whether and when full anticoagulation may be safely initiated. One author recommends waiting for at least 5 days after craniotomy.[202] If DVT is diagnosed and full anticoagulation is contraindicated, a vena caval filter should be placed. Thrombolytic therapy should not be considered if the patient has had intracranial or intraspinal surgery within the preceding 2 months.

Urologic Surgery

The incidence of DVT after urologic operations is similar to that following general surgery. Transurethral resections are associated with a much lower risk than open procedures. Mayo and colleagues[127] reported a 51% incidence of DVT in patients having open prostatectomy compared to a 10% incidence following transurethral resection of the gland. In their review of randomized clinical trials of the perioperative administration of low-dose heparin, Collins and associates[44] reported a 75% reduction in the risk of DVT in urologic patients treated with this form of prophylaxis. The NIH Consensus Conference recommended the use of low-dose heparin prophylaxis as the preferred method of DVT prophylaxis in urologic patients over the age of 40.[156] Despite these recommendations, there has been concern expressed regarding the safety and efficacy of low-dose heparin in certain procedures.[42, 143]

Coe and associates[42] compared the use of low-dose heparin to external pneumatic compression in a prospective randomized trial involving patients undergoing open urologic surgery. The boots were applied to the legs after induction of anesthesia and were continued until hospital discharge. The incidence of DVT documented by venography was 25% in the untreated control group, 21% in a low-dose heparin group, and 7% in patients receiving external pneumatic compression. In a similar patient population, Salzman and colleagues[181] demonstrated that the pneumatic compression boots could be discontinued when the patient was ready to ambulate, rather than at the time of hospital discharge, without a significant increase in the incidence of DVT. These limited data suggest that external pneumatic compression may be an attractive alternative to low-dose heparin in urologic patients.[42, 44]

Gynecologic Surgery

The incidence of DVT following gynecologic surgery is highly variable and is strongly influenced by the approach (vaginal or abdominal) and by the presence or absence of malignancy. In patients with benign disease, vaginal hysterectomy is associated with a 6% to 7% incidence of DVT whereas the incidence of this complication following transabdominal hysterectomy is 12% to 15%.[24, 212] The reported incidence of DVT in patients undergoing major pelvic surgery for malignant disease is between 12% and 33%.[39, 41] Other factors that influence the risk for developing DVT in gynecologic patients include the age of the patient, the duration of surgery, and a prior history of DVT.

Low-dose heparin significantly decreases the incidence of DVT in patients at moderate risk of developing this complication after gynecologic procedures. Two controlled studies have evaluated low-dose heparin in women undergoing major procedures for predominantly nonmalignant disease.[7, 203] Ballard et al[7] reported a 29% incidence of DVT in the control group compared to 4% in those receiving low-dose heparin, whereas Taberner et al[203] reported that 23% of control patients had DVT compared to 6% in those who were treated.

These benefits of low-dose heparin may not extend to the high-risk patient with malignant disease undergoing extensive pelvic surgery. Both retrospective and prospective studies have failed to demonstrate any reduction in the incidence of DVT with the use of low-dose heparin.[39, 40] External pneumatic compression may, however, be effective. Clarke-Pearson and colleagues[41] reported a threefold reduction in DVT when the boots were placed at induction of anesthesia and maintained for the first 5 postoperative days in patients undergoing pelvic surgery for the treatment of gynecologic malignancy.

The NIH Consensus Conference recommendations for the gynecologic patient are based on the anticipated risk for DVT.[156] Low-risk patients (those younger than 40 years of age undergoing procedures lasting less than 30 minutes) are satisfactorily managed with early ambulation combined with individually measured graduated compression stockings. Patients with nonmalignant disease but otherwise at moderate to high risk should receive low-dose heparin and pneumatic compression boots. The patient with gynecologic malignancy undergoing a major surgical procedure should be placed on pneumatic compression boots and dextran until fully ambulatory.

Cesarean delivery is associated with a moderate risk for DVT; although controlled studies are not available, the use of low-dose heparin or pneumatic compression boots may provide safe and effective prophylaxis.[156]

ORTHOPEDIC SURGERY

Prospective studies using venography have documented that an average of 52% of patients undergoing hip replacement and 66% of patients undergoing elective knee surgery develop DVT in the perioperative period.[87, 213] Venography is considered to be the gold standard for diagnosing DVT in this population, as noninvasive testing has proven to provide poor sensitivity and specificity.[92, 161] The usual low-dose heparin regimen may be less effective in orthopedic patients than in the general surgical population and is not usually recommended for prophylaxis.[74, 121] However, a recent review of all the randomized clinical trials comparing the use of low-dose heparin prophylaxis to no treatment reported a 56% reduction in the incidence of venographically documented proximal DVT in the treated group.[44]

The NIH Consensus Conference recommends the use of one of the following regimens in patients undergoing orthopedic surgery. Therapy should continue for at least 7 days or longer if the patient remains bedridden: (1) low-dose warfarin, (2) dextran 70, or (3) adjusted-dose heparin.[60, 121, 156] Other treatment options have been recently evaluated. They may be as effective, if not more so, than those recommended above. These include the combination of heparin and dihydroergotamine, low molecular weight heparin, or low molecular weight heparin with dihydroergotamine.[46, 54, 62, 102, 115, 164, 165, 208]

Patients undergoing other forms of elective orthopedic surgery such as ankle or arm procedures are at lower risk of developing DVT and can be managed with mechanical methods such as external pneumatic compression or graduated elastic stockings. The patient should be mobilized as quickly as possible in the postoperative period.

Despite multiple studies demonstrating significant decreases in the incidence of DVT and PE with the prophylactic use of various anticoagulants, they have not been widely accepted by orthopedic surgeons.[44] As mentioned above, this reluctance is caused primarily by the fear of bleeding at the surgical site. In patients undergoing elective joint replacement, increased bleeding may result in failure of the procedure.

Pneumatic leg compression does not increase the risk of bleeding; however, early reports suggested that it was not effective following total hip replacement. Gallus and colleagues[64] reported that pneumatic compression of the calf was ineffective in preventing proximal DVT in patients who had had hip prostheses, although it did prevent distal thrombosis. In contrast, Hull and associates[92] recently reported a significant decrease in the incidence of venographically documented DVT in a similar group of patients who received intermittent pneumatic leg compression of the calf and thigh beginning in the recovery room when compared to untreated controls. The total incidence of DVT in the treatment group was 24% compared with 49% in control patients, whereas the incidence of proximal DVT was 14% versus 27%.

The efficacy of pneumatic compression of the calf in preventing DVT in patients undergoing elective knee surgery was demonstrated in a study by Hull et al, [87] who found a 66% incidence of venographically documented DVT in a control group compared to an incidence of 6% in patients receiving calf compression.

Acceptance of intermittent pneumatic compression among orthopedic surgeons is likely to be greater than that of anticoagulant prophylaxis even though the incidence of DVT is somewhat greater when mechanical techniques are used.[92] A direct comparison of pneumatic compression with other prophylactic measures in orthopedic patients has not been published.

Patients with Trauma

Trauma patients are at high risk for developing DVT, and PE is one of the leading causes of late death in this population.[189] Injury may produce a transient hypercoagulable state secondary to the effects of circulating tissue thromboplastins and other procoagulant substances. When combined with venous stasis and endothelial injury, the stage is set for clot formation. There is a wide range in the reported incidence of DVT in trauma patients. In eight studies published between 1961 and 1985, the occurrence rate varied between 20% and 90%.[189] Much of this variability can be explained by the use of different methods for detecting thrombi and by inclusion of subgroups of patients with very high expected incidences of DVT in some of the studies, e.g., elderly patients with hip fractures or those with acute spinal cord injury. There are much fewer data regarding the risk of DVT in the more typical trauma patient, who is usually young and has sustained multiple injuries.

The average incidence of DVT in patients with hip fractures not receiving prophylaxis was 47% in nine studies conducted between 1965 and 1973.[130] Sevitt and Gallagher[186] found DVT in 83% of elderly patients who died following fractures of the femur. The majority of those who died from PE had undiagnosed DVT at autopsy. Several studies provide evidence that the duration of immobilization and bed rest play a more important role in the development of DVT in patients with hip fracture than the injury or surgical procedure.[63, 186, 197] In an autopsy study of patients with hip fractures, DVT was demonstrated in 19% of those who died within 4 days of injury, in 47% of patients who died in 4 to 7 days, and in more than 75% of those who survived for more than 1 week.[186] The finding that DVT is often bilateral in patients with unilateral hip fractures provides additional evidence supporting the importance of immobility in DVT formation.[186]

DVT is a common complication in patients with traumatic spinal cord injury, particularly if the injury results in paralysis.[29, 67, 146] Brach and colleagues[29] detected DVT in 90% of patients with acute spinal cord paralysis, whereas Myllynen and associates[146] reported DVT in 100% of their patients with similar injuries. In contrast, DVT is unusual if the patient remains neurologically intact.

The incidence of DVT in the general trauma population has been much more difficult to define. Fibrinogen scans are inaccurate in this population, as soft tissue injury and hematomas can produce false-positive scans. The presence of plaster casts and external fixation devices makes both subjective and objective evaluation for the presence of DVT difficult.[189] Venograms are the diagnostic procedure of choice; however, transport of these often critically ill patients to a radiology suite may be logistically difficult and is always potentially dangerous.

The young trauma victim who requires only a brief period of bed rest is likely to have a low incidence of DVT, although this has not been well documented. Shackford and associates[188] studied 177 patients with multiple trauma who had at least one risk factor for the development of DVT. Twenty-five patients in this study could not receive any form of prophylaxis; the incidence of the complication in this group was only 4%.

In contrast, patients with multiple trauma who require more prolonged immobilization are at substantial risk for the development of DVT. Kudsk et al[113] used venography to evaluate prospectively 38 patients who were immobilized for more than 10 days following injury. Although only one patient had clinical evidence of DVT, 63% had positive venograms, with clot extending above the knees in half of these patients.[113] The limited data available suggest that selected subgroups of patients with trauma appear to be at increased risk for DVT, and therefore some form of prophylaxis should be considered.[188, 189]

Patients with injuries to the lower extremities may begin developing thrombosis within hours of the traumatic event.[176] A thrombus may already be present when DVT prophylaxis is initiated; this factor may explain why standard low-dose heparin is ineffective in this setting.[176] The most appropriate method of DVT prevention in patients undergoing surgical repair of hip fractures remains controversial.[168] Full-dose oral anticoagulant therapy begun preoperatively is the most effective method for decreasing the risk of thromboembolic complications in these patients. However, as we have discussed above, anticoagulants are infrequently utilized by orthopedic surgeons because of the fear of hemorrhagic complications.[130, 168, 185] Powers and associates[168] compared the effects of aspirin to warfarin begun immediately postoperatively in patients with hip fractures. The agents were administered after surgery in an attempt to reduce the risk of operative and postoperative bleeding and to improve acceptance by orthopedists. A 10-mg dose of warfarin was given initially, with subsequent doses adjusted to raise the prothrombin time to 16 to 18 seconds. The incidence of DVT or PE was 20% in the warfarin group, 41% in the aspirin group, and 46% in a placebo group. No significant difference in bleeding complications was noted. Dextran infusions, external pneumatic compression, and individually fitted pressure gradient elastic stockings all appear to have some beneficial effects in patients with hip fractures.[156] Aspirin and other drugs with antiplatelet activity are ineffective.[141]

Recently, a low molecular weight heparinoid (Org 10172; Organon International, Oss, Holland) was compared to dextran 70 infusion in patients with hip fractures.[17] The heparinoid was begun preoperatively and continued postoperatively for 10 to 12 days. The venographically documented incidence of DVT was 12% in the Org 10172 group and 31% in the patients receiving dextran 70. The need for postoperative blood transfusion was significantly higher in the dextran 70 group. If these dramatic results are confirmed by future studies, it is likely that low molecular weight heparin or heparinoids will become the prophylactic measure of choice after traumatic injuries to the lower extremities.

Mechanical techniques such as external pneumatic compression or pressure gradient stockings remain the prophylactic methods of choice in patients following head trauma or spinal cord injury.[156] Standard low-dose heparin was compared to adjusted-dose heparin in patients with acute spinal cord injuries; treatment in this study was initiated more than 24 hours after injury.[67] Adjusted-dose heparin was much more effective in preventing thromboembolic disease (31% of the standard group versus 7% of the adjusted-dose group developed DVT); however, 24% of the adjusted-dose group required discontinuation, of treatment because of bleeding, compared to none of the low-dose group.[67]

Very little information is available regarding the efficacy and safety of the various forms of prophylaxis in the patient with multiple trauma. Ruiz and associates[176] evaluated 100 patients with multiple trauma and an injury-severity score greater than 10, and they found that low-dose heparin (5000 U every 12 hours) did not provide significant protection against DVT. The safety of more intensive anticoagulant treatment has not been established in this group of patients and is not recommended until the nature and extent of all injuries has been assessed, initial bleeding has been controlled, and the integrity of the hemostatic system has been restored.

Pneumatic compression boots are safe, but their efficacy has not been established in the patient with multiple trauma. Nonetheless, this prophylactic measure can be used in all higher-risk victims of trauma without fear of exacerbating bleeding and is recommended unless the presence of lower extremity trauma precludes their use.[156] Whether low molecular weight heparin or heparinoids are safe and effective in this population needs to be established.

TREATMENT

Once the diagnosis of DVT is established, full-dose heparin should be administered unless there are specific contraindications to its use. Heparin acts by combining with antithrombin III, a circulating anticoagulant protein produced in the liver. This complex rapidly neutralizes the proteolytic actions of the activated serine protease clotting factors. The rate of the clotting reaction decreases and less thrombin becomes available to catalyze fibrin formation. Other actions of heparin that may contribute to its antithrombotic effect include adherence of the agent to the vascular endothelium, producing a reduction in platelet adhesiveness.[163]

The usual initial dose of heparin is 10,000 U administered as an intravenous bolus, followed by either a continuous infusion of 1000 U per hour or intermittent injections of 5000 U every 4 hours. The risk of bleeding complications may be less with the use of continuous infusions.[180] The APIT should be maintained between 1.5 and 2.0 times control.[95] This value should be measured several times during the first day until the desired therapeutic goal has been achieved.[95] Subsequently, only daily measurements are required. Sensitivity to heparin is influenced by the activity of the thrombotic process. A higher dose of heparin is required to achieve a therapeutic APTT in patients with symptomatic proximal DVT on account of a greater concentration of activated clotting factors than is found in patients with smaller peripheral thrombi.

Therapy with heparin is generally continued for 7 to 10 days, by which time deep venous thrombi either resolve or organize. If risk factors for the development of DVT are still present, anticoagulation must be continued. Oral coumarin derivatives such as warfarin are frequently used for long-term prophylaxis in such patients. Anticoagulant therapy is usually continued for 1.5 to 6.0 months following the development of proximal DVT in the perioperative period.

After initiation of warfarin treatment, complete anticoagulant protection is delayed for several days while vitamin K stores and the normal vitamin K–dependent clotting factors are eliminated. They are subsequently replaced by biologically inactive factors. Because factor VII has the shortest biologic half-life, its depletion results in prolongation of the prothrombin time, but because this factor is of minor importance in the pathogenesis of DVT, protection is insufficient.[163] By the fourth day of warfarin therapy, factors IX and X are depleted and the patient will then be adequately anticoagulated. Heparin should therefore be continued for at least 4 days after the initiation of warfarin treatment.[11] An increased risk of venous thrombosis may exist during the first 2 days of warfarin use as a result of depletion of protein C, a vitamin K–dependent factor with anticoagulant properties and a half-life of 4 to 6 hours.[163, 211] Overlapping heparin and warfarin therapy should minimize this risk. An initial warfarin dose of 10 mg orally followed by daily doses of 5 mg for the next 3 days is the usual regimen.

Subsequent doses should be adjusted according to the prothrombin time, which should be maintained at 1.2 to 1.5 times control.[84, 85] The optimal time interval between the initial heparin bolus and the first dose of warfarin has not been clearly defined. Recent studies have demonstrated that beginning warfarin early in the course of therapy of DVT and PE can decrease the length of hospitalization without an increased frequency of thromboembolic complications.[94, 139, 174]

Thrombocytopenia may develop in up to 30% of patients receiving heparin. This is usually a mild and transient decrease in the platelet count that improves during continued heparin use and is of no clinical consequence.[116] The mechanism appears to be related to a heparin-induced release of adenosine diphosphate (ADP) that produces reversible platelet aggregation, margination, and peripheral sequestration.

A severe, immunologically mediated form of thrombocytopenia occurs in 0.6% to 10% of patients receiving heparin.[116] Heparin combines with a component of the platelet membrane to form a hapten that stimulates the production of platelet membrane antibodies.[193] Seven to 14 days after initiation of heparin therapy, thrombocytopenia develops accompanied by arterial thrombosis and hemorrhagic phenomena. This reaction is associated with a mortality of 18% to 36% and a morbidity of 22% to 61% if the drug is not discontinued.[116, 193] If it is necessary to stop the administration of heparin, alternative forms of anticoagulation should be used.[193] Because of the danger of this complication, the platelet count must be determined before initiation of therapy, daily for the first 2 days, and then once every 2 or 3 days.

Warfarin interacts with many drugs, and many clinical conditions alter its effect. Therefore, it is more difficult to regulate the anticoagulant effect of this agent than that of heparin (Table 2). Guidelines for the use of anticoagulants for the treatment of DVT are summarized in Table 3.

Thrombolytic agents such as streptokinase and urokinase can be used to treat DVT and may be associated with more rapid clinical improvement and less morbidity than are seen following the use of heparin, but their use is contraindicated within 10 days of surgery. The paucity of controlled, randomized clinical trials demonstrating a decreased incidence of PE or postphlebitic syndrome, and the increased potential for significant hemorrhagic complications, has limited the use of these agents for the treatment of DVT.[103] (See also article by Dehring.)

Inferior Vena Caval Interruption

Inferior vena caval interruption interferes with the propagation of emboli originating in the deep veins of the legs. Early surgical attempts at the prevention of recurrent pulmonary embolism included bilateral ligation of the common femoral veins and infrarenal ligation of the inferior vena cava. Unfortunately, these procedures were associated with substantial morbidity; recurrent pulmonary embolism via collat-

Table 2. WARFARIN INTERACTIONS

Enhancers* **(prolongs prothrombin time)**	**Suppressors†** **(decreases prothrombin time)**
Allopurinol	Adrenal corticosteroids
Anabolic steroids	Barbiturates
Clofibrate	Cholestyramine
Diphenylhydantoin	Diuretics
Disulfiram	Griseofulvin
Hepatic disease	Haloperidol
Hypermetabolic states	Hereditary resistance
Low vitamin K diet	High vitamin K diet
Metronidazole	Oral contraceptives
Phenylbutazole	Rifampin
Salicylates	Uremia
Trimethoprim-sulfamethoxazole	

*Warfarin dose may need to be decreased.
†Warfarin dose may need to be increased.
Modified from Hyers TM: Antithrombotic therapy for venous thromboembolism. Clin Chest Med 5:479, 1984; with permission.

erals and venous stasis were the two most frequent complications.[23] Perioperative mortality rates averaged approximately 15%.[123]

Attempts were subsequently made to occlude the inferior vena cava partially in order to prevent massive pulmonary embolization, whereas at the same time decreasing the risk of venous stasis. Suture and staple plication techniques were introduced, but because a laparotomy was still required in an often critically ill patient, morbidity and mortality remained high, although they were lower than following complete inferior vena caval interruption.[23]

In 1968, intraluminal techniques were introduced that did not

Table 3. GUIDELINES FOR ANTITHROMBOTIC THERAPY WITH HEPARIN AND WARFARIN IN VENOUS THROMBOEMBOLISM

- Disease suspected
  - Measure baseline APTT, PT, and platelet count and give heparin bolus, 10,000 U IV
  - Order diagnostic test, e.g., V̇/Q̇ scan, pulmonary angiogram, venogram
- Disease confirmed
  - Give additional dose of heparin (5000 U) and start constant IV infusion at 1000 U/h
  - Monitor APTT at 4–6 h intervals until it is stabilized between 1.5 and 2.0 times control value
  - Monitor platelet count while administering heparin
  - Start warfarin by day 2 or 3 giving 10 mg, followed by a daily maintenance dose PO (2.5–10 mg)
  - Continue heparin for at least 7–10 days
  - After at least 4–5 days of combined therapy, stop heparin and check PT 4 hours later
  - Maintain PT off heparin at 1.2 to 1.5 times control or pretreatment value (using rabbit brain thromboplastin)
  - Continue full-dose anticoagulation for at least 3 months in patient without continuing risk factors, longer in other patients

From Kaufman B: Deep vein thrombosis and pulmonary embolism in the injured patient. *In* Capan LM, Miller SM, Turndorf H (eds): Trauma: Anesthesia and Intensive Care. Philadelphia, JB Lippincott, 1991, p 832; with permission.

require abdominal surgery or general anesthesia.[199] Although a number of devices have been described, the largest experience has been gained with the Greenfield filter. This device can be placed through the femoral or internal jugular vein, which may be entered by surgical cutdown under local anesthesia or by percutaneous puncture under radiographic control.[162] The cone shape of this filter permits it to be filled with clot up to 80% of its depth before a pressure gradient develops.[199] This central trapping and capture of emboli, with continued caval flow, helps explain why venous stasis and recurrent embolization occur much less frequently than following complete vena caval interruption. Recurrent PE is an uncommon event following Greenfield filter placement, with an estimated frequency of 1% to 4%.[33, 68, 107] Long-term patency of the vena cava is found in approximately 97% of patients.[33, 68, 107] Significant complications of filter placement are infrequent. They include filter migration, caval perforation producing retroperitoneal hematoma, incorrect initial filter position, leg edema, and thrombosis of the inferior vena cava. The Greenfield filter is constructed so that the curved prongs of the struts engage and become anchored to the caval wall. When the filter is released from the introducer, it may perforate the cava at the point of engagement; it may fail to engage the vessel wall when the caval diameter exceeds 30 mm, resulting in embolization of the filter into the right heart, or it may engage asymetrically.

Carabasi and associates[33] reported on a series of 198 Greenfield filter placements in 193 patients. Major postoperative complications occurred in 4.1%, with the most common problem being thrombosis of the inferior vena cava. Recurrent pulmonary embolism developed in 1%. Greenfield and Michna[68] reviewed their 12-year clinical experience with the filter and reported that there was no direct surgical mortality resulting from filter insertion.

The four most common indications for interruption of the inferior vena cava are (1) contraindication of anticoagulant therapy, (2) hemorrhagic complications of anticoagulant therapy, (3) recurrent pulmonary embolism despite "adequate anticoagulation," and (4) prophylaxis in patients at high risk of developing thromboembolism.[23, 59] Other less common indications include massive pulmonary embolism when the patient is unlikely to survive any further obstruction of the pulmonary vascular bed and following embolectomy. As recent studies have documented the long-term efficacy and safety of the Greenfield filter, indications for its placement have been liberalized. Some authors have suggested that the Greenfield filters should be placed in patients with free-floating thrombi in the inferior vena cava or iliac veins, as the risk of these clots embolizing is substantially higher than that of adherent clots; however, a consensus has not been reached on this recommendation.[6, 20, 153] The Greenfield filter should also be considered as primary therapy of thromboembolic disease in any patient at increased risk of hemorrhagic complications of anticoagulation, such as those with metastatic carcinoma and the elderly.[43, 161]

Surgical Treatment

The role of surgery in the treatment of DVT is limited to catheter thrombectomy of the ileofemoral venous system when the immediate or long-term function of the involved limb is threatened.[18, 123] This option should be considered in patients with evidence of massive swelling and pain in the leg. Initially arterial pulsations are normal and the leg may have a pale appearance (phlegmasia alba dolens). If leg edema progresses, arterial inflow may decrease and venous gangrene may develop. This presentation of ileofemoral DVT, called *phlegmasia cerulea dolens,* is seen in 2% to 10% of all patients with ileofemoral thrombosis and requires immediate treatment. Conservative treatment includes leg elevation, fluid resuscitation, and full heparinization. Thrombolytic therapy should be considered unless contraindications are present. If venous gangrene is present, or if phlegmasia alba dolens is progressing to phlegmasia cerulea dolens, immediate thrombectomy may be limb and life saving.[18]

ANESTHETIC TECHNIQUE AND DEEP VEIN THROMBOSIS

The choice of anesthetic technique may play a critical role in the prevention of DVT. It has been recently recognized that the use of spinal or epidural anesthesia for certain types of surgical procedures is associated with a decreased incidence of postoperative DVT.[133]

The occurrence of DVT following elective total hip replacement with the use of general anesthesia is as high as 75% to 80%.[101] Thorburn and associates[206] demonstrated that patients undergoing this procedure under spinal anesthesia had a significantly lower incidence of DVT than those receiving a general anesthetic. Modig and colleagues[138] prospectively evaluated patients undergoing total hip replacement and documented a rate of DVT of 44% in patients who received lumbar epidural anesthesia with continuation into the postoperative period compared with 83% of those who had general anesthesia. Proximal DVT was significantly less common in the epidural group (65% versus 17%, $P = 0.001$). The incidence of postoperative pulmonary embolism was also significantly lower after epidural anesthesia.

The beneficial effects of regional anesthesia on the occurrence of thromboembolic disease have also been demonstrated in patients undergoing other types of orthopedic procedures. For example, patients undergoing repair of femoral neck fractures had a significantly lower incidence of postoperative DVT following spinal anesthesia than after general anesthesia.[56, 127] Similar results were reported when lumbar epidural anesthesia was compared to general anesthesia in patients undergoing total knee replacement.[99, 152, 190]

The evidence supporting a beneficial role of regional anesthesia in the prevention of DVT is not as conclusive for urologic and general surgical procedures. Hendolin and associates[76] found a 12% incidence of DVT in patients undergoing retropubic prostatectomy with epidural anesthesia compared to a 51% incidence when general anesthesia was used. However, when the same group compared the effects of thoracic epidural anesthesia to general anesthesia in patients undergoing cholecystectomy, no significant differences in the incidence of DVT were found, although there was a trend toward a lower incidence of DVT in the regional anesthesia group.[77] Because the occurrence of postoperative DVT in the general surgical population is much lower than in orthopedic patients, a considerably larger cohort of general surgical patients would be required to demonstrate a statistically significant difference in the incidence of thromboembolic complications. Thoracic epidural anesthesia may be less effective than lumbar epidural anesthesia for DVT prophylaxis, because these techniques have different effects on lower extremity blood flow (these are discussed in the next section).[122] Several other studies have failed to demonstrate a decrease in the incidence of postoperative DVT following a regional technique.[16, 34, 61, 62, 129] However, other prophylactic measures were used in these studies (e.g., dextran 70, heparin).[16, 34, 61, 62] In addition to lowering the overall frequency of DVT, these prophylactic measures may also obscure any potential additional benefit provided by the use of regional anesthesia. The results of studies comparing the effects of regional to general anesthesia on the incidence of DVT are summarized in Table 4.

Lower Extremity Blood Flow

The difference in the incidence of DVT between regional and general anesthesia may be explained by the effects of these techniques on lower extremity blood flow. The rate of lower extremity arterial inflow, venous emptying, and venous capacity are all greater during continuous lumbar epidural anesthesia than during general anesthesia, probably as a result of the vasodilatation produced by the regional techniques.[122, 137, 191] In addition, induction and maintenance of general anesthesia reduces the velocity of blood flow in the femoral vein.[73, 166] Positive-pressure ventilation may play a major role in this effect, because it may increase impedance to venous return and decrease cardiac output. The flow velocity in the femoral vein is reduced by approximately 40% with the induction of general anesthesia, whereas lumbar epidural anesthesia increases flow velocity by 120%.[166] This hyperkinetic state may counteract the tendency toward thrombus formation in the perioperative period. The institution of continuous thoracic epidural anesthesia is not associated with increased lower extremity blood flow; this may explain why a significant reduction in the incidence of postoperative DVT has not been demonstrated with the use of this technique.[129, 194]

Table 4. STUDIES COMPARING REGIONAL AND GENERAL ANESTHESIA IN TERMS OF DVT OUTCOME

Author/ Reference	Procedure	N	Type of Anesthesia	Incidence of DVT (%)	*P*
Thorburne et al[206]	Hip replacement	85	SA vs GA	29 vs 53	<0.05
Davis et al[56]	Femoral neck fracture	74	SA vs GA	46 vs 76	0.05
Modig et al[136]	Hip replacement	30*	LEA vs GA	33 vs 73	NSS
			(proximal DVT)	20 vs 73	<0.05
Hendolin et al[76]	Retropubic prostatectomy	38	LEA vs GA	12 vs 51	<0.02
Hendolin et al[77]	Cholecystectomy	98	TEA or TEA+GA vs GA	7 vs 13	NSS
Mellbring et al[129]	Major abdominal	50	TEA+GA vs GA	38 vs 38	NSS
Modig et al[135]	Hip replacement	60*	LEA vs GA	40 vs 77	<0.01
			(proximal DVT)	13 vs 67	<0.001
McKenzie et al[127]	Femoral neck fracture	40	SA vs GA	40 vs 75	<0.05
Modig et al[138]	Hip replacement	94*	LEA vs GA	44 vs 83	<0.001
			(proximal DVT)	17 vs 65	<0.001
Wille-Jorgensen (1989)[215]	Hip replacement	98	LEA vs GA	9 vs 31	<0.03
Davis et al[55]	Hip replacement	140	SA vs GA	13 vs 27	<0.05
Nielsen et al[152]	Knee replacement	36	LEA vs GA	15 vs 63	<0.05
Jorgensen et al[99]	Knee replacement	49	LEA vs GA	18 vs 59	0.02
Sharrock et al[190]	Knee replacement	541	LEA vs GA	48 vs 64	<0.001

Abbreviations: SA = spinal anesthesia; GA = general anesthesia; LEA = lumbar epidural anesthesia; TEA = thoracic epidural anesthesia; NSS = not statistically significant.

*Interim reporting of ongoing clinical trial.

Effects on Coagulation

Epidural anesthesia is known to inhibit the neuroendocrine stress response to major surgery or trauma.[12, 30, 108] Among the features of the stress response are an increase in blood coagulability and a depletion of plasma fibrinolytic activity.[12, 187] One would therefore expect less alteration in these factors in patients undergoing surgery with epidural anesthesia.

Factor VIII capacity (a measure of coagulation) increases significantly in patients undergoing total hip replacement with either epidural or general anesthesia. However, the level of this response is significantly lower postoperatively following epidural anesthesia. Blood fibrinolytic activity decreased by the third postoperative day after a general anesthetic, whereas no change was detected in patients who had had epidural anesthesia.[134] Ephedrine (50 mg) was given subcutaneously prior to institution of epidural anesthesia in this study. In addition, the local anesthetic solution contained 5 μg/mL of epinephrine. These sympathomimetic agents increase plasminogen activator release, which enhances fibrinolysis.[125] This may be an important factor in reducing thrombus formation in the postoperative period. Plasma fibrinolytic activity was measured prior to surgery in patients receiving either epidural or general anesthesia. Fibrinolytic activity was significantly greater in the epidural group than in the general anesthesia group.[134] When epinephrine is not added to the epidural solution and prophylactic ephedrine is omitted, this increase in fibrinolytic activity is not observed.[78]

Therefore, epidural anesthesia appears to produce a decrease in the incidence of postoperative DVT by at least 3 mechanisms: (1) increased lower extremity blood flow velocity, (2) decreased coagulability secondary to blocking of the stress response to surgery, and (3) enhancement of fibrinolysis by added sympathomimetic agents.[132]

Blood Transfusion

Another factor that may influence postoperative coagulation status is related to the necessity for blood transfusion. Many studies have demonstrated a lower average blood loss when the patient receives a spinal or epidural anesthetic than when general anesthesia is administered.[1, 48, 61, 206] The resultant decreased need for transfusion is probably related to the lower mean arterial blood pressure seen with regional techniques, although the increased venous pressures seen during general anesthesia as a result of positive-pressure ventilation may also play a role. Studies have demonstrated that banked blood becomes deficient in antithrombin-3 with increasing storage time. Multiple blood transfusions can thus deplete plasma fibrinolytic activity and lead to an increased risk of postoperative DVT.[187]

Local Anesthetic Effects

In addition to the effects already described, there may be properties intrinsic to the local anesthetic agents themselves that lower DVT risk. Cooke and associates[49] infused intravenous lidocaine at a rate of 2 mg/min for 6 days after elective hip surgery. The incidence of DVT was 14% in the treatment group compared to 78% in the controls. There were no significant differences between the groups in intraoperative blood loss, transfusion requirements, postoperative coagulation tests, or fibrinolytic activity.

In vivo studies have demonstrated inhibition of platelet aggregation in the presence of local anesthetics.[154] It has been demonstrated in vitro that lidocaine, bupivacaine, and tocainide exert antiaggregatory effects on platelets exposed to ADP and collagen. These effects were more pronounced after prolonged incubation times.[25] This inhibition of platelet aggregation has been suggested as a possible mechanism for the lower incidence of postoperative DVT in patients receiving regional anesthetics. This effect may explain the results obtained in the study by Cooke and colleagues[49] in which high blood levels of local anesthetic would be expected. However, anesthetic blood levels obtained during continuous lumbar epidural anesthesia are less than the 10 to 25 μg/mL concentrations necessary to affect platelet function.[25] Grant et al[66] have demonstrated that the blood concentrations usually achieved by epidural local anesthetics do not inhibit platelet aggregation.

The primary effect of local anesthetics on coagulation may be mediated by improved blood viscosity rather than by the effects on platelet aggregation.[191] Local anesthetics can impair leukocyte locomotion and thereby decrease white cell adherence to the vascular endothelium, limiting thrombus formation.[198] There may also be an effect on endothelial cells, with increased formation of prostacyclin and decreased formation of thromboxane.[35]

In summary, a decreased incidence of DVT associated with spinal and epidural anesthesia has been demonstrated in a variety of studies. This beneficial effect is most likely secondary to a combination of factors. The use of a regional anesthetic exerts effects on lower extremity blood flow and blood viscosity, coagulation, and fibrinolysis. The inhibition of the stress response may also be partially responsible, as well as the direct effects of local anesthetic agents on platelets, leukocytes, and endothelial cells. Sympathomimetic agents, either combined in the local anesthetic solution (e.g., epinephrine) or given prophylactically at the institution of epidural anesthesia (e.g., ephedrine) may also exert an effect. Although a variety of mechanisms are involved, the use of a regional anesthetic has been shown to lower the risk of DVT and even of pulmonary embolism in high-risk surgical patients.

Regional Anesthesia and Anticoagulant Therapy

The presence of a coagulopathy is often cited as a contraindication to regional anesthesia.[216] The primary concern is the potential for uncontrollable bleeding that could lead to epidural hematoma and subsequent paraplegia.

The role of anticoagulation in the formation of epidural hematoma is not entirely clear. Cases of epidural hematoma have been ascribed to the use of regional techniques in anticoagulated patients.[158, 205] However, this complication has also been reported in anticoagulated patients who have not received a regional anesthetic; thus, the anesthetic may in fact be an incidental event in a case of spontaneous bleeding.[53] To complicate matters further, postoperative patients receiving neither anticoagulation nor regional anesthesia have also developed spontaneous epidural hematomas.[148]

Because of these confounding variables, the actual risk of performing a regional anesthetic in the anticoagulated patient or in the patient who is to receive intraoperative anticoagulation is difficult to assess. No controlled clinical trials are available to quantify the risk of this complication. However, a number of studies in various clinical scenarios may help to sort out the risks.

Regional Anesthesia and "Full" Anticoagulation

Patients who are receiving therapeutic doses of anticoagulants, or who have recently been treated with a thrombolytic agent, present an absolute contraindication to the use of a regional technique.[58, 158, 205] If the therapy can be withheld or reversed preoperatively and appropriate studies reflect the return of normal coagulation, spinal or epidural anesthesia should present no additional risk.[155]

Regional Anesthesia and "Low-dose" Anticoagulation

Subcutaneous heparin for prophylaxis of DVT is a common therapy for hospitalized patients. A significant number of these patients require surgical intervention and might be candidates for a regional anesthetic. It seems that spinal or epidural anesthesia is not contraindicated in the presence of preoperative heparin prophylaxis, as several studies have reported the lack of complications under these circumstances.[2, 200] Odoom and Sih[155] placed 1000 epidural catheters prior to vascular surgery in 950 patients who had been receiving oral anticoagulant therapy preoperatively. The anticoagulant dose was decreased on the day prior to surgery and omitted on the day of the operation. Patients were excluded from the study if the preoperative thrombotest (TT) was less than 10% of control; i.e., within the therapeutic range. Therefore, some reversal of anticoagulation was required for inclusion in the study (mean preoperative TT was 19 + 0.23%). Patients were also excluded if they had a history of blood dyscrasias, prior heparin therapy, or aspirin therapy of long duration. Catheters were then inserted not more than 3 to 5 cm into the epidural space, and small doses of heparin were maintained via infusion for the duration of the procedure. There were no reported cases of epidural hematoma or neurologic sequelae.

The results of this study suggest that the risk of epidural hematoma from regional anesthesia in the anticoagulated patient is minimal. However, a much larger population may be necessary to determine the incidence of this complication. In addition, Metzger and Singbastl[131a] recently reported that two patients who were receiving "mini-dose" heparin developed epidural hematoma following continuous epidural anesthesia. It is possible that prophylactic heparin played an important role in the development of the hematoma. Although this complication might have developed spontaneously, the report places some doubt on the belief that epidural anesthesia is without risk under these conditions. Thus, regional anesthesia in the presence of prophylactic anticoagulant therapy appears to be safe only in the absence of a history of coagulopathy or use of drugs that alter normal coagulation and in the presence of normal clotting studies performed shortly before administration of the anesthetic. (See also article by Dehring.)

The surgical patient who is treated with aspirin or nonsteroidal anti-inflammatory agents often presents a difficult choice for the anesthesiologist. When a regional anesthetic is the preferred method, it would seem best to withhold aspirin for 7 to 10 days or the anti-inflammatory agent for 48 to 72 hours prior to surgery. When such therapy cannot be discontinued for an appropriate period of time, the history, physical examination, and appropriate laboratory tests may help in the anesthesiologist's decision. The role of a bleeding time determination in this setting is controversial.[80] Therefore, firm recommendations cannot be made for this subset of patients.

Regional Anesthesia and Intraoperative Anticoagulation

Rao and El-Etr[171] reported on 4011 patients receiving regional anesthesia for vascular surgery. All of the patients were given intraoperative anticoagulation; none of them developed an epidural hematoma. It is important to recognize that several steps were taken to minimize the risk of a hemorrhagic complication: (1) patients were excluded from the study if a blood dyscrasia or thrombocytopenia was present or if they had been receiving preoperative anticoagulants; (2) if blood was aspirated from the needle or catheter upon insertion, the surgery was postponed for 24 hours and then performed under general anesthesia; (3) heparin therapy was begun 50 to 60 minutes after completion of the block and given in 500-U increments with close monitoring of the activated clotting time; and (4) the catheters were removed 24 hours after insertion, 1 hour before the first maintenance dose of heparin was given. If these strict guidelines are followed, it appears that intraoperative anticoagulation in the presence of an epidural catheter is safe. A recent retrospective review of 912 patients and the previously discussed work of Odoom and Sih support the results of Rao's group.[10, 155] Available data suggest that an anticipated need for intraoperative anticoagulation should not be considered a contraindication to the performance of a regional anesthetic.

SUMMARY

Deep venous thrombosis is a common syndrome in hospitalized surgical patients. Its presence places the patient at significant risk for pulmonary embolism. Surgery and general anesthesia increase the risk for DVT. Prevention or early treatment of DVT will markedly decrease the incidence of pulmonary embolism. Many measures have been utilized to decrease the incidence of DVT. Pharmacologic methods that may be effective include low-dose heparin, coumarin, and dextran. Intermittent pneumatic leg compression is an effective mechanical method for DVT prophylaxis.

Surgical patients can be classified as low, moderate, or high risk for perioperative thromboembolic complications. The requirement for, and choice of, prophylactic method should be influenced by the estimated risk for DVT and the nature of the surgical procedure.

The anesthetic technique also influences the risk of DVT. The use of spinal or epidural anesthesia for certain types of surgical procedures is associated with a decreased incidence of postoperative DVT. The choice of anesthetic technique may be influenced by the concurrent treatment of established DVT or the use of DVT prophylaxis with anticoagulants. Regional anesthesia is usually avoided in the fully anticoagulated patient but is probably safe when the patient is receiving "low-dose" heparin prophylaxis if the hemostatic system is otherwise intact.

Familiarity with the pathophysiology and management of DVT is essential for optimal perioperative management of the surgical patient.

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PULMONARY THROMBOEMBOLISM

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The clinical spectrum of thromboembolic disease in surgical patients ranges from asymptomatic deep vein thrombosis (DVT) to death from massive pulmonary thromboemboli (PTE). Because DVT is frequently asymptomatic and clinical signs are mainly nonspecific, DVT should be suspected when risk factors are present. In one series of patients dying from PTE, premortem diagnosis was made in only 5%. Associated DVT was found at autopsy in 83% of those with PTE, but only 3% of the DVT was diagnosed before death.[166]

Anesthesiologists tend to focus on PTE, but DVT is its often silent precursor. Characteristic clinical presentations arouse the suspicion of PTE, but less than half of patients with "typical" PTE symptoms actually show positive pulmonary angiograms.[140,155] High-risk patients may frequently have asymptomatic or silent PTE.[201] Nevertheless, an autopsy study has shown that mortality from PTE decreased from 8.8% to 2.3% of surgical deaths between 1966 and 1981. The lower mortality was attributed to the increased use of anticoagulants or possibly a changing pattern of occurrence.[51] A recent prospective multicenter trial, in which a vast majority (94%) of patients with proven PTE received treatment, demonstrated that only 2.5% of the patients died directly from PTE.[21a] Although mortality rates within 1 year of PTE and during hospital stay were 23.8% and 9.5%, respectively, most deaths were caused by underlying diseases. Cancer, infection, cardiac disease, and chronic lung disease rather than PTE appeared to be the most frequent causes of death in this study.[21a]

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RISK FACTORS FOR DVT AND PTE

The risk factors (stasis, hypercoagulability, and vessel injury) described by Virchow over a century ago still apply to DVT developing in the perioperative period. In one study, almost one third of patients older than 40 years of age undergoing intra-abdominal surgery exhibited calf vein thromboses. Half of these small thrombi actually formed during the surgical procedures.[97] Intraoperative venodilation (stasis), demonstrated by ultrasonography, correlated with a higher incidence of postoperative DVT.[34] The venoconstrictor, dihydroergotamine, given with heparin decreased both venous distension and the occurrence of DVT following surgery.[33]

Primary (congenital) hypercoagulability results from an excess of coagulation factors, the presence of abnormal anticoagulants, and deficient or nonfunctional anticoagulants. Abnormal anticoagulants include lupus anticoagulants, which are antibodies that form against phospholipids and paradoxically increase both the partial thromboplastin time and the risk of thromboses.[13] Anticoagulant factors that may be deficient or nonfunctional include (1) plasminogen or other fibrinolytic proteins; (2) antithrombin III, the heparin cofactor that neutralizes activated clotting factors II (thrombin), IX, X, XI, and XII; and (3) protein C and its cofactor protein S, two vitamin K–dependent proteins that neutralize activated factors V and VIII.[169]

Secondary hypercoagulable states develop from surgical procedures, pregnancy, cancer, anticoagulant protein loss (nephrosis), or consumptive coagulopathy.[169] Ironically, heparin can cause a secondary hypercoagulable state by excessive consumption of its cofactor antithrombin III[121] or by inducing platelet antibodies, which cause thrombocytopenia and platelet aggregation with resultant arterial and venous thromboses.[25]

Direct vessel damage occurs in 10% to 20% of hip surgery procedures and during pelvic surgery. This trauma can induce isolated femoral or pelvic vein thromboses, which are not associated with calf vein thrombi.[28, 76, 171]

The risk of DVT is higher in the presence of advanced age, obesity, malignancy, congestive heart failure, acute myocardial infarction, prolonged immobilization, or paralysis.[36] The incidence and mortality rate of DVT and PTE have been demonstrated to increase exponentially after age 59.[5] Young patients, including children, may develop DVT from trauma, surgery, prolonged immobilization, cancer, pregnancy, estrogen use, infection, congenital heart disease, or chronic medical diseases.[20, 36]

Hull et al[89] presented a simple classification of risk factors for DVT in surgical patients. Low-risk patients are those younger than 40 years of age undergoing uncomplicated surgery or over 40 years of age who require minor surgery. General surgery patients over 40 years old who are undergoing a procedure lasting longer than 30 minutes are considered to have a moderate risk of DVT. These patients exhibit an incidence of calf vein thrombosis of 10% to 40%, proximal vein thrombosis of 2% to 10%, and fatal PTE of 0.1% to 0.7%. High-risk patients include those undergoing orthopedic procedures on the lower limbs, those over age 40 undergoing extensive pelvic or abdominal surgery for malignancy, and those with a recent history of thrombophlebitis.[89] Open prostatectomies[124] and lower extremity amputations[200] also are associated with high rates of thrombotic complications. Calf vein thrombosis occurs in 40% to 80%, proximal vein thrombosis in 10% to 20%, and fatal PTE in 1% to 5% of these high-risk patients.[89] The risk of developing DVT does not end after hospital discharge for patients older than 40 years who have undergone major abdominal surgery. One fourth of these patients discharged without DVT developed this complication within 6 weeks after leaving the hospital.[170]

The techniques and drugs designed to prevent DVT and PTE, summarized in Figure 1, are discussed elsewhere in this issue (see article by Kaufman and Young) and have recently been reviewed.[26, 31, 35, 88, 96, 129, 145, 146, 165]

ORIGIN OF EMBOLI

An estimated 90% of PTE originate from venous thrombi in the large lower extremity and pelvic veins.[178] Most commonly, they begin as calf vein thrombi, which can propagate into the larger popliteal, femoral, and pelvic venous systems,[97] but DVT can also form in femoral or pelvic veins after vessel trauma.

Thrombi may also embolize from the right heart as a result of

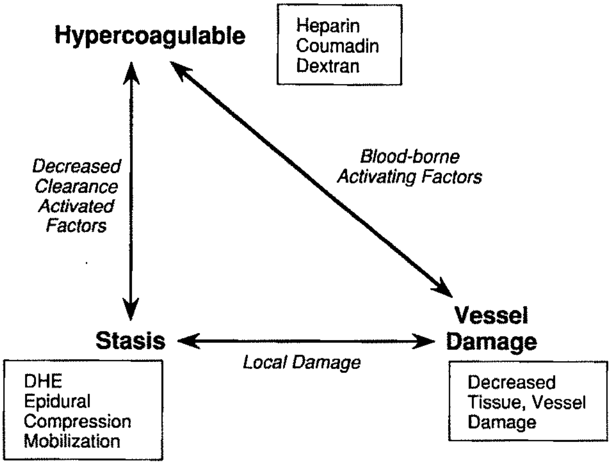

Figure 1. The three causes of deep vein thromboses as originally recognized by Virchow are represented with the prophylactic techniques (in boxes) that affect each of the three causes. Compression could be provided by well-fitting stockings or external pneumatic compression devices. DHE is dihydroergotamine.

congestive heart failure, atrial fibrillation, indwelling foreign bodies, tricuspid endocarditis, or rarely after myocardial contusion.[184] Emboli originating from renal, hepatic, or upper extremity vein thromboses are rare and are usually associated with clinically apparent disease.

Calf Vein Thrombosis

Calf vein thrombi that are detected by radiolabeled fibrinogen scanning are generally considered too small to cause fatal PTE. The concern with these small blood clots is that 20% of them propagate into the larger femoral and pelvic veins.[97, 156] When calf vein thrombi are symptomatic, the risk of proximal propagation and embolization is increased, and heparin or oral anticoagulant therapy is needed.[105] Recent studies, however, have shown that untreated outpatients with clinically suspected DVT,[85] as well as ambulatory and hospitalized patients with abnormal, non–high probability lung scans,[87] can be safely monitored for proximal extension of the thrombi. Impedance plethysmography was performed four to five times over 10 to 14 days in these two groups of patients. The 3% to 5% of patients who developed proximal vein thrombi were anticoagulated and the remainder safely avoided anticoagulation.[85, 87]

Inferior Vena Cava or Femoral "Floating" Thrombi

Despite adequate heparinization, recurrent emboli occur in 27% of patients with free-floating thrombi in the inferior vena cava (IVC) and in 17% of those with thrombi attached to the IVC.[136, 160] Free-floating femoral vein thrombi, demonstrated by noninvasive ultrasound scanning, also embolize more often than those that are adherent. Heparin therapy is continued or an IVC filter may be inserted until serial monitoring demonstrates attachment of the femoral vein thrombi—a process that requires an average of 9.2 days (range, 4–18 days).[11]

Central Vein or Right Heart Thrombosis

Thromboses detected by echocardiography in the right atrium or ventricle are associated with a mortality of 31%, as demonstrated by a recent meta-analysis.[103] The death rate was lower for adherent thrombi and those induced by central venous catheters than it was for migrating PTE. Anticoagulation with heparin gave slightly better survival rates than either embolectomy or thrombolytic therapy.[103]

DIAGNOSIS OF PTE AND DVT

Pulmonary Angiography

Pulmonary angiography is the gold standard for diagnosing PTE. The possibility of mortality (0.2%) and morbidity (3.5%)[132] has led to some reluctance to request this study. It should be remembered, however, that mortality from unnecessary use of heparin is higher than that from performing pulmonary angiography.[14, 24] The indications for pulmonary angiography include (1) discrepancies between the clinical index of suspicion and interpretation of a ventilation/perfusion ($\dot{V}/\dot{Q}$) scan, (2) intermediate or indeterminate results of $\dot{V}/\dot{Q}$ scan (perfusion defect associated with infiltrate on chest roentgenogram, (3) complex therapeutic implications (recent surgery, high risk of bleeding), (4) high-probability $\dot{V}/\dot{Q}$ scans when anticoagulants are contraindicated, (5) coexisting diseases that mimic PTE (lung cancer, pneumonia), and (6) unstable patients with possible massive PTE (candidates for embolectomy or thrombolytic therapy).[141]

Relative contraindications to pulmonary angiography include elevated right ventricular end-diastolic pressure (RVEDP), severe pulmonary hypertension, bleeding disorders, contrast dye allergy, renal insufficiency, and left bundle branch block.[141] An RVEDP of greater than 20 mm Hg is associated with a 3% mortality from pulmonary angiography. In patients with severe pulmonary hypertension and systemic hypotension, it is probably safer to perform angiography only when indicated by $\dot{V}/\dot{Q}$ scan results. The use of low rather than the conventional high ionic contrast material may be preferable in these circumstances.[141, 153]

Ventilation/Perfusion Scans and Other Diagnostic Techniques

Perfusion scans may be used to estimate the probability of PTE based on the anatomic distribution of injected radiolabeled albumin. This test is associated with a high rate of false-positive results if it is interpreted by itself. Its diagnostic power may be improved by combining it with a simultaneously obtained chest roentgenogram, a ventilation scan performed following inhalation of ^{133}-xenon, or both. Criteria have been developed to define high, low, and intermediate or indeterminate probabilities of PTE[164a] based on the size of the perfusion defect and the presence or absence of matching ventilation scan and chest roentgenogram abnormalities (Table 1). The ventilation scan and chest roentgenogram help in differentiating between PTE- and non–PTE-induced perfusion defects. For example, a large perfusion defect without associated abnormalities of the chest roentgenogram and ventilation scan suggests a high probability, whereas a small perfusion defect with abnormal roentgenogram or ventilation scan findings indicates a low probability of PTE (Table 1).

The accuracy and usefulness of $\dot{V}/\dot{Q}$ scans in the diagnosis of PTE have been until recently a matter of controversy, partly because of a lack of scientifically rigorous studies to assess the sensitivity and specificity of these tests.[88, 101, 122] A recent multicenter trial (Prospective Investigation of Pulmonary Embolism Diagnosis or PIOPED study), which involved comparison of $\dot{V}/\dot{Q}$ scans and pulmonary angiograms of more than 900 patients with clinically suspected PTE, determined

Table 1. CRITERIA USED FOR PROBABILITY ASSESSMENT OF ACUTE PULMONARY THROMBOEMBOLISM (PTE)*

Category	Scintigraphic and Roentgenographic Criteria
No probability of PTE	No perfusion defects. On the perfusion scan the shape and boundaries of the lung are similar to those seen on the chest roentgenogram (chest roentgenogram, ventilation scan or both may be abnormal.)
Low probability of PTE	Nonsegmental perfusion defects. Single moderate-size mismatched perfusion defect with normal chest roentgenogram. A perfusion defect that is substantially smaller than parenchymal abnormality on the chest roentgenogram. Large or moderate-size perfusion defects that involve no more than four segments in one lung or three segments in one lung region. There are matching ventilation defects as large as or larger than the perfusion defects. The chest roentgenogram may be normal or may show abnormalities that are substantially smaller than the perfusion defects. Perfusion defects involving more than three segments with a normal chest roentgenogram. (Perfusion defects involving less than three segments with a normal chest roentgenogram indicate a very low probability of PTE.)
Intermediate (indeterminate) probability of PTE	$\dot{V}/\dot{Q}$ scan and chest roentgenographic findings that cannot be interpreted as low- or high-probability PTE or are classified as borderline high- or borderline low-probability PTE.
High probability of PTE	Two or more moderate- or large-size segmental perfusion defects without corresponding ventilation scan or chest roentgenogram abnormalities or with substantially larger than matching ventilation scan or chest roentgenogram abnormalities. Four or more moderate-size segmental perfusion defects without ventilation scan or chest roentgenogram abnormalities.

*Criteria used in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) Study. *Modified from* Rubinstein E: Thromboembolism. Sci Am Med I:XVIII, page 4, 1991; with permission.

the degree of diagnostic reliability provided by scintigraphy and shed some light on this controversial issue.[155] Negative perfusion scans, which are generally considered a reliable exclusion criterion for PTE and an indication for holding the heparin therapy,[88, 101] were associated with PTE in 4% of the patients in the PIOPED study.[155] On the other hand, the vast majority of patients with angiographically proven PTE had positive $\dot{V}/\dot{Q}$ scans ranging from low to high probability. Scans were, however, also positive in many patients whose clinically suspected PTE could not be substantiated by the results of pulmonary angiogram. Thus, $\dot{V}/\dot{Q}$ scans generally have high sensitivity (98%) but low specificity (10%) in diagnosing PTE.

The diagnostic power of high-, low-, and intermediate-probability scans varies considerably. Of the 251 patients with angiographically proven PTE in the study, only 102 (41%) had high-probability $\dot{V}/Q$ scans, although 97% of patients with high-probability scans did have PTE. The false-positive high-probability scans that reduced the specificity of the test from 100% to 97% were generally seen in patients with a previous history of PTE. Intermediate- (indeterminate-) and low-probability scans were, respectively, associated with angiographically proven PTE in 33% and 12% of instances. Thus, it is clear that $\dot{V}/Q$ scans interpreted alone do not have absolute diagnostic accuracy, although a negative scan suggests the absence of PTE, whereas a high-probability scan indicates its presence with a high likelihood. Intermediate- and low-probability scans are of little help in the diagnosis of PTE.[155]

The accuracy of $\dot{V}/\dot{Q}$ scans may be improved if their results are combined with those obtained from clinical symptoms and signs. Significant clinical indicators in combination with $\dot{V}/\dot{Q}$ scan results established the diagnosis in 96% of instances in the PIOPED study.[155] PTE could also be excluded at the same rate of accuracy (96%) if the clinical impression and $\dot{V}/\dot{Q}$ scan results showed a low probability for the disease. Unfortunately, a clear agreement between clinical status and scan results occurs infrequently, and pulmonary angiography is often required to establish the diagnosis.

Magnetic resonance imaging (MRI) and computed tomography (CT) have been used to diagnose PTE, but they have not been verified as primary diagnostic tools. Central PTE and intravascular filling defects can be detected with CT. Evaluation of chest roentgenogram abnormalities by CT scan has been used to detect pulmonary infarction secondary to undiagnosed PTE.[172] The utility of MRI in PTE diagnosis is limited by the test's long duration and the difficulty of managing critically ill patients within the magnetic field. Both central and peripheral PTE can be detected by MRI, but its sensitivity compared with pulmonary angiography is unknown. MRI may be used to determine if pulmonary hypertension is caused by PTE and whether the PTE is acute or chronic.[172] Digital subtraction angiography is a sensitive technique that uses less contrast material than pulmonary angiography. Patients must be still and hold their breath for 5 to 10 seconds, since this technique is sensitive to motion artifact.[12]

The diagnosis of PTE should ideally be established by pulmonary angiography before the patient undergoes a pulmonary embolectomy, because 70% to 100% of patients have died when this procedure was performed with an incorrect preoperative diagnosis.[27, 37] In urgent circumstances, diagnoses have been made with echocardiography or after injecting contrast dye via central venous or pulmonary artery catheters.[48, 167] Bedside pulmonary angiograms have been performed in unstable patients using a flow-directed pulmonary angiography catheter (NOT Swan-Ganz) and portable chest roentgenograms.[164]

Unusual phenomena may be observed in patients with PTE who have pulmonary artery catheters. These include (1) the inability to measure the cardiac output when the thermistor of pulmonary artery catheter is occluded by an embolus,[117] (2) a visualization of kinking of the catheter on chest roentgenogram after placement,[1] (3) the presence of both pulmonary hypertension and an unobtainable pulmonary capillary wedge pressure (PCWP),[185] and (4) an "overwedge" tracing (large increase in pulmonary artery pressure) after deflation of the balloon, presumably from entry of the catheter tip into the embolus.[57]

Invasive and Noninvasive Diagnoses of DVT

Venography is the gold standard for diagnosing DVT. However, noninvasive tests that serially monitor the venous system are becoming more prevalent. The impedance plethysmogram and Doppler ultrasound are relatively sensitive and specific noninvasive techniques predominantly useful for detecting proximal vein thromboses.[34, 82, 198] Impedance plethysmography detects the impedance changes to a small electrical current when the leg blood volume is altered by inflating and deflating a pneumatic cuff on the thigh. Venous obstruction is demonstrated by a flatter curve during deflation. Doppler ultrasonography detects augmented venous flow by an increase in sound intensity during compression of the calf or distal thigh. Duplex B-mode ultrasonic images have recently been used to display real-time images of thrombi or of blood flowing through proximal leg veins.[115]

The detection of proximal DVT by those noninvasive techniques has been a major diagnostic advance, since it has diminished the number of pulmonary angiograms performed following equivocal $\dot{V}/\dot{Q}$ scans. Deep vein thrombosis is present in 70% of patients with suspected PTE,[86] and is treated in the same way, i.e., with heparin and oral anticoagulation. Bone[15] has recently suggested a schema for the use of noninvasive tests to minimize the need for pulmonary angiography (Fig. 2).

The radiolabeled fibrinogen scan is useful for the serial assessment of prophylactic therapy. The limitations of this test include the 24 hours needed for fibrin deposition, lower sensitivity for proximal vein thromboses, the unknown significance of asymptomatic calf vein thrombosis, and false positives from accumulation of radioactivity in surgical wounds, particularly after hip surgery.[82, 198]

SIGNS AND SYMPTOMS

Pulmonary thromboembolism is difficult to diagnose because its symptoms and signs may be nonspecific in previously healthy patients, whereas it may mimic cardiopulmonary complications in chronically ill, high-risk patients. Three common presentations of PTE are (1) dyspnea, (2) pulmonary infarction with pleuritic pain and hemoptysis, and (3) hemodynamic collapse or syncope.[5, 112, 179]

Dyspnea, tachypnea, tachycardia, apprehension, rales, cough, accentuated pulmonic heart sound, or chest pain that may be pleuritic or angina-like are each observed in more than 50% of patients in several

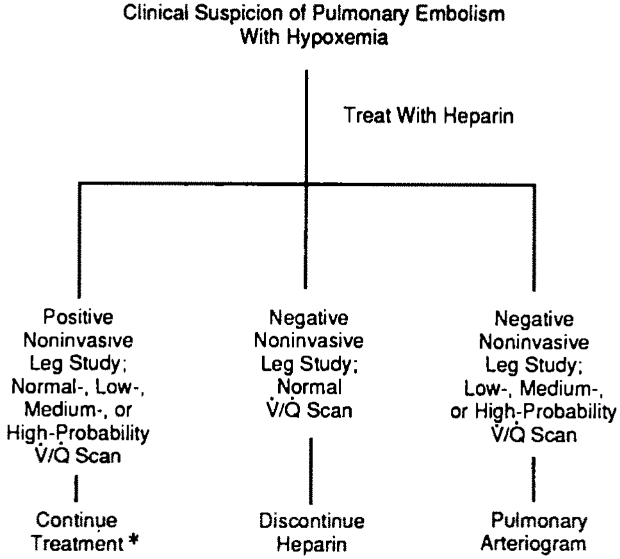
Clinical Suspicion of Pulmonary Embolism
With Hypoxemia
Treat With Heparin
Positive Noninvasive Leg Study; Normal-, Low-, Medium-, or High-Probability V̇/Q̇ Scan
Negative Noninvasive Leg Study; Normal V̇/Q̇ Scan
Negative Noninvasive Leg Study; Low-, Medium-, or High-Probability V̇/Q̇ Scan
Continue Treatment *
Discontinue Heparin
Pulmonary Arteriogram

Figure 2. Bone's schema for diagnosis of suspected pulmonary embolism maximizes the use of noninvasive diagnostic techniques. The asterisk indicates that treatment should be continued only if a high-quality noninvasive leg study can be performed. In selected cases with very high suspicion of pulmonary embolism (i.e., persons with previous documented pulmonary embolism), a high-probability ventilation/perfusion (V̇/Q̇) scan might be accepted as proof of pulmonary embolism without an angiogram. (*From* Bone RC: Ventilation/perfusion scan in pulmonary embolism—"the emperor is incompletely attired" [editorial]. JAMA 263:2794, 1990; with permission.)

large series. Hemoptysis, low-grade fever, cyanosis, diaphoresis, signs of elevated central venous pressure, clinical DVT, syncope, or altered mental status occur in 10% to 40% of patients with PTE. Wheezing, disseminated intravascular coagulation, and abdominal pain resulting from infarcted lung on the diaphragm are seen rarely.[5, 112, 180]

A multivariate analysis has selected 16 factors that predicted 71% of both positive and negative diagnoses in surgical and medical patients.[22] The relatively rare finding of neck vein distension was the strongest discriminating variable. Increasing age, obesity, basilar chest pain, recent surgery, mental obtundation, fever, tachypnea, a history of palpitations, collapse, sudden onset of cough, the presence of third or fourth heart sounds, and an elevated hemidiaphragm correlated positively with a diagnosis of PTE. A history of cardiac disease, leg pain, prolonged cough, and atrial fibrillation correlated negatively with PTE.[22]

Chest Roentgenogram, ECG, and Laboratory Tests

The chest roentgenogram and ECG can exclude other acute catastrophes, but when present, changes are generally nonspecific or transient. The most common ECG abnormalities associated with PTE include nonspecific ST-T changes, atrial or ventricular rhythm disturbances, and right ventricular abnormalities, such as right bundle branch block, $S_1Q_3T_3$, right atrial strain, and right (or occasionally left) axis deviation.[150, 180]

Chest roentgenogram changes after PTE include infiltrates, pleural effusion, atelectasis, or elevation of a hemidiaphragm owing to pneumoconstriction.[21] Infiltrates may persist for several weeks but usually resolve. The persistent wedge-shaped infiltrates resulting from pulmonary infarction occur predominantly in patients with chronic cardiac or pulmonary diseases that impair venous drainage or in those who have abnormal bronchial circulation.[42] A rare, slightly more specific finding of acute PTE is Westermark's sign, a dilated pulmonary artery in the hilum with oligemia in its distal distribution. A normal chest roentgenogram in a severely dyspneic, hypoxemic patient also suggests PTE.[21]

No laboratory tests have been found to be specific for diagnosing PTE. Preliminary studies indicate that plasma DNA measurement is a promising test if patients with diseases that elevate DNA are excluded. This test has a specificity of 82% and a sensitivity of 85%.[190]

CARDIOPULMONARY CHANGES AFTER PTE

Respiratory Changes

Hypoxemia and hypocapnia are characteristic of PTE. However, the severity of hypoxemia cannot distinguish between patients with positive or negative pulmonary angiograms.[69] Unfortunately, a Pa_{O_2} above 80 or even 90 mm Hg does not exclude the diagnosis of PTE.[90, 140] The tachypnea induced by the embolic event overcompensates for even a massive increase in deadspace ventilation (>50%) and thus typically yields hypocarbia.[43, 83]

The $\dot{V}/\dot{Q}$ mismatch has been evaluated by the multiple gas elimination technique. Excess perfusion to lung units with low $\dot{V}/\dot{Q}$ ratios is a prominent abnormality,[83] presumably related to redistribution of blood flow away from the embolized areas or to bronchoconstriction in nonembolized lung areas.[83] The true intrapulmonary shunt (flow through nonventilated areas) was surprisingly low, but the calculated venous admixture was 27%.[83] Another mechanism of hypoxemia following PTE is impairment of hypoxic pulmonary vasoconstriction caused by the pulmonary hypertension.[59] A further decrease in Pa_{O_2} may result from right to left shunting through a patent foramen ovale.[43, 114, 148]

Hypoxemia in the patient with subacute PTE is most likely caused by localized atelectasis resulting from hypoxemia, hypocarbia, or decreased surfactant production in the embolized lung segments.[38] The intrapulmonary shunt fractions determined by the multiple inert gas elimination technique have been shown to correlate with the severity of the atelectasis on chest roentgenogram in patients with subacute PTE[82] (see also article by Dantzker).

Hemodynamic Changes

The magnitude of the hemodynamic changes caused by PTE correlates in healthy patients with the size of the embolus. Patients with PTE and no prior cardiopulmonary disease exhibited a mean pulmonary artery pressure (PAP) of 22 mm Hg when 30% of the vasculature was obstructed and of 36 mm Hg with 50% occlusion. PAP did not increase above 40 mm Hg in any previously healthy patient; a higher value implied preexisting cardiopulmonary disease.[128] The central venous pressure (CVP) was above 5 mm Hg in most previously healthy patients with greater than 35% vessel obstruction from PTE. However, the CVP was not always elevated even in the face of massive occlusion.

The cardiac index (CI) also did not correlate with the magnitude of the PTE. The CI tended to be elevated, probably as a result of the sympathetic nervous system response to the hypoxemia seen when the patient was breathing room air. However, this value was less than 2.3 L/min/m^2 in three of five patients with more than 50% of the vasculature obstructed.[128] Another study examined five previously healthy patients with emboli involving more than 50% of the vasculature. The CI averaged 2.2 L/min/m^2, and the CVP and RVEDP were 13 to 14 mm Hg with normal PCWP. On the other hand, the gradients between pulmonary artery diastolic pressures and PCWP were always greater than 5 mm Hg and averaged 11 mm Hg.[93]

No correlation was found between the size of the PTE and the magnitude of change in the CI, PAP, or CVP in patients with underlying cardiopulmonary disease.[127] Small PTE could severely depress the CI or increase the mean PAP to over 40 mm Hg in these chronically ill patients. The PCWP was commonly elevated in patients with a history of congestive heart failure.[127]

Right Ventricular Failure

The thin-walled, compliant right ventricle (RV) can fail after PTE because the RV afterload increases dramatically. Severe pulmonary hypertension shifts the ventricular septum toward the left ventricle (LV). Both LV volume (preload) and LV compliance thereby decrease.[99] Right-sided coronary artery perfusion pressure is greatly reduced as a result of the systemic hypotension and elevated RVEDP. In addition, RV distension limits right-sided coronary flow to only diastole instead of the normal flow that takes place during both systole and diastole.[19] The resultant RV ischemia can lead to further systemic hypotension, RV dilation, and LV impairment, in what Guyton described as the "vicious circle" of RV failure.[75] Further RV decompensation results if tricuspid regurgitation or flow through a patent foramen ovale are induced by these events[54] (see also article by Dries and Mathru in this issue).

SUPPORTIVE TREATMENT OF PTE

Oxygenation and Ventilation

Supplemental oxygen is routinely provided to treat the arterial and tissue hypoxemia resulting from PTE. However, supplemental oxygen may not sufficiently increase PaO_2 because of the low mixed venous oxygen tension ($M\bar{V}O_2$) and the severity of the $\dot{V}/\dot{Q}$ mismatch. Increasing the cardiac output is therefore critical to improving oxygenation. A mathematical model has been used to demonstrate that an increase in the cardiac output should increase the $M\bar{V}O_2$ from 27 to 40 mm Hg and raise the PaO_2 from 61 to 87 mm Hg.[83]

When mechanical ventilation is necessary because of hemodynamic instability or to treat inadequate PaO_2, the ventilator settings may need to be different from those used to treat pulmonary edema. Initially, a small tidal volume (7 mL/kg) and rapid respiratory rate without positive end-expiratory pressure (PEEP) should be employed to minimize airway pressures and RV afterload.[90, 149] If hypoxemia from PTE is treated with progressive increases in PEEP, the additional stress on the already impaired RV may produce hemodynamic deterioration. PEEP shifts the ventricular septum to the left, increases RV wall stress, and decreases venous return, LV volume, and cardiac output.[92] Careful monitoring of the CI, $M\bar{V}O_2$, and PaO_2 is therefore necessary to apply PEEP safely in patients with PTE. However, PEEP may benefit these patients if ventilation to excessively perfused lung zones increases without a decrease in CI or $M\bar{V}O_2$. PEEP is probably useful for treating subacute PTE, in which atelectasis is a prominent cause of the hypoxemia.[202]

Volume Administration

Volume administration to patients with PTE may be beneficial or deleterious, depending on the RV compliance before the fluids are given. Titrated infusion of colloidal solutions has been shown to improve cardiac output and systemic pressure in patients with PTE.[77, 149] However, hemodynamic collapse may also result from massive RV dilation following volume infusion.[109] Fluid administration thus should be titrated to a CVP (RV preload) of 12 to 15 mm Hg to avoid RV failure. However, CI may continue to improve with higher CVP. Thus, fluid administration may be cautiously continued so long as the CI continues to improve. Fluid infusion must be stopped if the CVP increases precipitously or CI decreases. No studies have compared colloids and crystalloids in PTE, but colloidal solutions may be advantageous. Colloids provide a greater and more persistent increase in blood volume and, therefore, a lower volume of solution is required.[72]

Inotropes

Selection of an inotropic agent depends on the severity of the hemodynamic compromise.[48, 54, 157] Isoproterenol, which functions as a pulmonary vasodilator, bronchodilator, and β-agonist, is appropriate for treating mild hemodynamic compromise from PTE. Patients with more severe dysfunction may deteriorate as a result of isoproterenol-induced tachycardia, systemic vasodilation, or arrhythmias.[17]

The efficacy of dobutamine and dopamine has been compared in previously healthy, volume-resuscitated patients with massive PTE. Dobutamine was considered preferable to dopamine. Both drugs effectively increased CI and mean arterial pressure, but dopamine also increased PAP and heart rate.[91] However, dopamine is indicated when elevation of cerebral and coronary perfusion pressures is necessary.

No clinical studies describe the use of epinephrine or norepinephrine for treating PTE. Case reports and experimental studies support the efficacy of norepinephrine in severe RV failure, in which elevation of right-sided coronary perfusion pressure is critical. A bolus (100 μg) and titrated infusion of norepinephrine increased the cardiac output and blood pressure of an elderly man with PTE who was unresponsive to high-dose dopamine.[158] Norepinephrine improved RV failure, as well as renal function, in dogs embolized with blood clots.[6] The α-agonist properties of this agent appeared to be most important, since phenylephrine also decreased the RVEDP, increased MAP, CI, and coronary blood flow, and reversed the right-sided cardiac ischemia.[194]

The use of inotropes in the presence of limited RV outflow can result in some unusual but easily explained hemodynamic changes. Increasing the CI may actually increase the PAP owing to a higher blood flow through the restricted pulmonary arterial system. A decrease in PAP must be correlated with the CI, since this change may indicate either pulmonary vasodilation or a severely decreased CI. Ironically, an increased CI may actually decrease the Pa_{O_2}. This phenomenon is attributed to increased intrapulmonary shunt fraction from greater perfusion of areas with low $\dot{V}/\dot{Q}$ ratios. Despite the lower Pa_{O_2}, tissue perfusion improves, as indicated by the higher tissue oxygen delivery and mixed venous oxygen content.[90]

Vasoactive Mediators

Pulmonary hypertension from PTE results from both mechanical obstruction and release of vasoactive and bronchoactive mediators. PTE obstructing half of the pulmonary vasculature has been shown to induce a mean PAP of 35 mm Hg,[128] whereas unilateral mechanical occlusion of a pulmonary artery increased PAP to only 23 mm Hg.[199] Vasoactive mediators, including serotonin and thromboxane, are released as a result of activation of platelets and clotting factors, such as thrombin.[183] Heparin improves cardiopulmonary function by preventing further release of these pulmonary vasoconstrictors and bronchoconstrictors.[183] Heparin administration is, therefore, recommended before the definitive diagnosis of PTE is made[38, 149] if contraindications are not present.

The serotonin antagonist ketanserin was given to 10 heparinized patients who had non–life-threatening PTE ($FIO_2 = 0.21$).[84] The PaO_2 increased by 6 mm Hg and the PAP and MAP decreased by 3 and 9 mm Hg, respectively, with unchanged CI. Some patients with larger, more recent emboli tended to show greater improvements in oxygenation and pulmonary vasodilation.[84] Ketanserin may have more dramatic effects in patients who have not received heparin.

Pulmonary vasodilation should theoretically increase the CI in patients with PTE. However, pulmonary vasodilating drugs are nonspecific. Concomitant dilation of the systemic circulation could severely compromise hemodynamic stability. Nitroglycerin has been used to treat pulmonary hypertension from oleic acid infusion in dogs. This agent was safer and more effective than nitroprusside, which induced systemic hypotension.[152] Nifedipine and hydralazine have been used by angiographers to decrease pulmonary hypertension but no specific details of their efficacy were provided.[18] Combinations of an alpha-agonist and a pulmonary vasodilator, such as norepinephrine and prostaglandin E_2, have been used to treat RV failure after cardiac surgery.[39] Such drug combinations are probably appropriate for managing the hemodynamic compromise from PTE. Hydralazine has been found to be an effective and relatively specific pulmonary vasodilator in hemodynamically compromised, embolized dogs,[53] but caution is indicated because of its systemic vasodilator properties.

DEFINITIVE TREATMENT OF PTE

Massive PTE obstructs 40% to 50% of the pulmonary vasculature. However, clinical outcome has been shown to correlate with hemodynamic response rather than embolus size.[81] Patients presenting with clinical shock had a mortality of 22% to 33% versus 5% to 8% in those without shock.[4, 81, 140]

An algorithm for treating surgical patients who have no contraindications to anticoagulation is presented in Figure 3.[48] Treatment options vary depending on whether the patient is stable or unstable or if the emboli are central or peripheral. Contraindications to anticoagulants limit therapeutic options (Fig. 4).[48] Clinical judgment about the urgency of the situation, local resources, and contraindications to thrombolytic therapy should determine the management of the individual patient.

Heparin

Heparin decreases mortality from PTE.[8] The death rate has been found to be 8% for treated and 32% in untreated patients.[4] A heparin bolus (typically 5000 U) is recommended before definitive diagnosis is made, assuming there are no contraindications, to prevent additional accumulation of platelets and thrombin on the embolus. Continuous

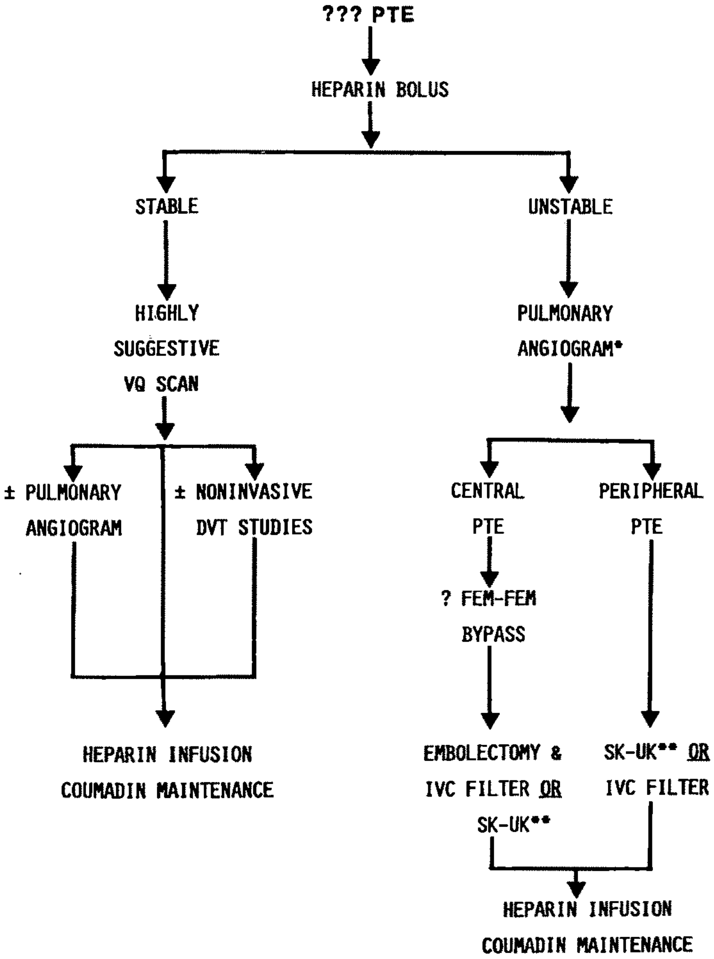
??? PTE
HEPARIN BOLUS
STABLE
UNSTABLE
HIGHLY SUGGESTIVE VQ SCAN
PULMONARY ANGIOGRAM*
± PULMONARY ANGIOGRAM
± NONINVASIVE DVT STUDIES
CENTRAL PTE
PERIPHERAL PTE
? FEM-FEM BYPASS
HEPARIN INFUSION COUMADIN MAINTENANCE
EMBOLECTOMY & IVC FILTER OR SK-UK**
SK-UK** OR IVC FILTER
HEPARIN INFUSION COUMADIN MAINTENANCE

Figure 3. This algorithm represents the management of patients with no contraindications to anticoagulants. The branch points depend on whether the patients are stable or unstable, with central or peripheral emboli. * = V/Q scan useful if negative; **PTT = must be normal in patients after SK-UK before starting heparin. SK-UK = streptokinase and urokinase. (*From* Dehring DJ, Arens JF: Pulmonary thromboembolism: Disease recognition and patient management. Anesthesiology 73:146, 1990; with permission.)

infusions of heparin are generally started at a rate of 1000 to 1500 U/h to maintain the partial thromboplastin time at 1.5 to 2.0 times normal. Increased doses are required during the initial treatment of PTE, because of greater heparin clearance.[175]

Bleeding is the most feared complication of heparin administration. Mortality rates from heparin have ranged from 0% to 3%, and major bleeding has been reported in 0% to 33% of anticoagulated patients.[14] Major hemorrhage occurred in 1.3%, and the total incidence of bleeding was 9% in a recent prospective study of 2656 heparinized patients.[196]

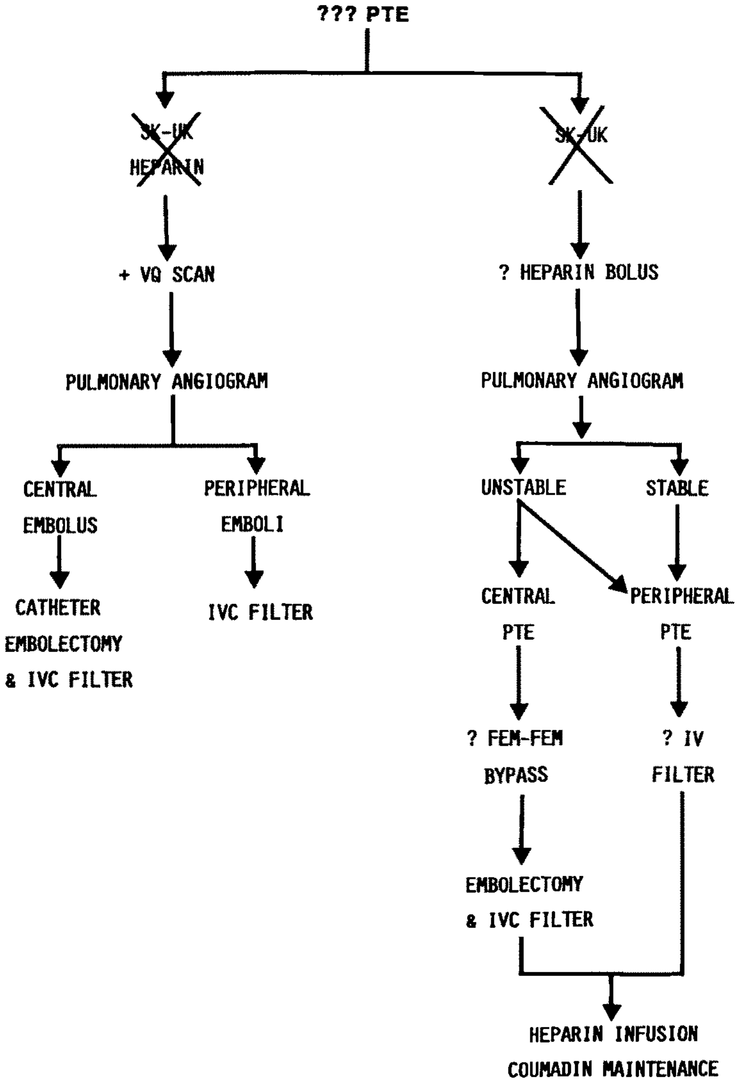

Figure 4. An algorithm for the management of patients with contraindications to anticoagulants. The branch points are contraindications, represented by X, to SK-UK (streptokinase-urokinase) or to heparin. Open embolectomy or catheter embolectomy can be performed for central PTE. Femoral-femoral arteriovenous bypass can be initiated before anesthetic induction. Peripheral PTE should be managed only by placing an inferior vena cava (IVC) filter to prevent additional emboli from reaching the lung. (*From* Dehring DJ, Arens JF: Pulmonary thromboembolism: Disease recognition and patient management. Anesthesiology 73:146, 1990; with permission.)

Major bleeding was seven times higher in alcoholics, and its incidence tripled in patients older than 60 years or in those receiving higher doses. This complication was twice as common in patients using aspirin, in those with a BUN over 50 mg/dL, and in female patients. Major complications tend to be related to risk factors, whereas minor bleeding episodes are associated with higher heparin doses.[196]

Low molecular weight heparin, which theoretically should produce fewer bleeding complications, was compared with standard heparin for the treatment of PTE, DVT, or axillary vein thrombosis.[2] Low molecular weight heparin more selectively activates factor X, with less thrombin activation and platelet binding than standard heparin. Half of the patients studied were at risk for bleeding and about 20% had had surgery within 10 days. Low molecular weight heparin was an effective anticoagulant but bleeding complications were decreased by only a nonsignificant 21%.[2]

Heparin induces antibodies to platelets, with resultant platelet aggregation and thrombocytopenia, in about 0.5% to 10.0% of patients. A large series has shown that bovine heparin induced platelet antibodies in 11.4% of patients, whereas these antibodies were seen in only 2.5% of those receiving porcine heparin.[197] Thrombocytopenia usually develops after 6 to 12 days of high-dose therapy and rarely occurs with low-dose heparin.[197] It can result in hemorrhagic complications or devastating venous and arterial thrombi from platelet clots.[7, 25, 107, 197] A recent survey conducted in a teaching institution over a 3-year period has identified 169 patients who developed thrombocytopenia subsequent to receiving heparin. Antibody formation was confirmed by testing plasma for the ability to induce platelet aggregation.[107] The morbidity rate from heparin-induced antibodies was 22.5% and the mortality was 12.0%. Eight complications were hemorrhagic and 30 were thrombotic; 28 of the patients with thrombosis required surgery.[107]

Immediate treatment for heparin-associated thrombocytopenia includes stopping the agent and using oral anticoagulants or an inferior vena cava filter to prevent further PTE. Fibrinolysis has also been used to treat these thrombi.[197] Continuing heparin therapy is risky once platelet antibodies are identified. Three patients in the previously quoted study had no complications, but one patient needed a femoral embolectomy for a white thrombus and another eventually died from colonic bleeding.[107] Adrenal insufficiency secondary to adrenal thrombosis is a rare complication of heparin-associated thrombocytopenia.[177]

Reexposure to heparin for surgical procedures or treatment of recurrent PTE typically induces thrombocytopenia in patients with a history of platelet antibodies, although the time course varies. Thrombocytopenia occurs acutely if antibodies are still circulating, or in 1 to 2 days if antibodies are induced by an amnestic response.[197] Platelet aggregation tests using normal platelets and patient plasma can be performed to determine if antibodies are still present.[107] It should be noted that low molecular weight heparin also produces sensitization; 2 of 25 patients receiving this preparation developed thrombotic complications.[193]

Many different protocols have been used in small numbers of patients with prior heparin-associated thrombocytopenia who require heparin. Plasmapheresis for 5 days removes platelet antibodies before heparin administration.[191] The prostacyclin analogue, Iloprost,[104] dextran, or coumadin[176] have been safely substituted for heparin. Administering the antiplatelet drugs aspirin or dipyrimadole before heparin prevented thromboses, but thrombocytopenia still occurred.[107, 108, 176]

Thrombolytic Therapy

Thrombolytic therapy with urokinase, streptokinase, or tissue plasminogen activator (TPA) should be considered for PTE with hemodynamic instability, in which the rate of clot lysis is critical. However, the National Cooperative Study could not show decreased mortality from PTE treated with thrombolytic agents compared to those receiving heparin. Initially, thrombolysis was faster with urokinase than with heparin, but the resolution of the embolus at 1 week was similar.[140] The risk of bleeding was about three times higher with streptokinase than with heparin.[68] Surgery, vaginal delivery, or invasive procedures within 10 days of treatment are major relative contraindications to the use of thrombolytic agents. Active bleeding or recent intracranial processes (within 2 months) are absolute contraindications to thrombolysis (Table 2).[142] Unfortunately, no laboratory tests can predict which patients will develop hemorrhagic complications during thrombolytic therapy.[80]

Many dosage schedules have been devised to optimize clot lysis and minimize hemorrhagic complications from thrombolytic therapy.

Table 2. CONTRAINDICATIONS TO THROMBOLYTIC THERAPY

Absolute Contraindications
Active internal bleeding
Recent (within 2 months) cerebrovascular accident or other active intracranial process
Relative Major Contraindications
Recent (<10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
Recent serious gastrointestinal bleeding
Recent serious trauma
Severe arterial hypertension (>200 mm Hg systolic or >110 mm Hg diastolic)
Relative Minor Contraindications
Recent minor trauma, including cardiopulmonary resuscitation
High likelihood of a left heart thrombus, e.g., mitral disease with atrial fibrillation
Bacterial endocarditis
Hemostatic defects including those associated with severe hepatic or renal disease
Pregnancy
Age > 75 years
Diabetic hemorrhagic retinopathy

From NIH Consensus Conference: Thrombolytic therapy in thrombosis: A National Institutes of Health Consensus Development Conference. Ann Intern Med 93:141, 1990.

Selected protocols are summarized in Table 3. However, only the doses of urokinase (4400 IU/kg loading, 4400 IU/kg × 12 hours) and streptokinase (250,000 U loading, 100,000 U/h × 24 hours) used in the National Cooperative Study[140] and a TPA dose of 100 mg over 2 hours are approved by the Food and Drug Administration for the treatment of PTE.

Two regimens have been selected for detailed discussion in this article because they were used in patients with life-threatening hemodynamic compromise[154] or included postoperative patients.[192] Fourteen nonsurgical patients with life-threatening PTE (clinical shock, RV failure, syncope, or seizures) received a urokinase bolus (15,000 IU/kg) through pulmonary angiography or right atrial catheters.[154] A 30% improvement in hemodynamic and angiographic parameters occurred within 3 hours in the 12 patients who exhibited a fibrinolytic state. The two patient deaths, which included one patient with no fibrinolysis, were not caused by bleeding complications. No serious hemorrhagic diathesis occurred in these 14 unstable patients[154] or in an additional 9 stable patients treated with this regimen.[50]

TPA was developed with the hope that it would induce less

Table 3. SELECTED THROMBOLYTIC REGIMENS*

		Dose			**Bleeding %**
Drug	**N**	**Loading**	**Maintenance**	**Improvement**	*Total (Serious)*
UK[189]	59	4400 IU/kg IV	4400 IU/kg/hr × 12 hr	P. angio 45% at 24 hr	51 (17)
SK[189]	54	250,000 U IV	100,000 U/hr × 24 hr	P. angio ~ 40% at 24 hr	32 (19)
UK[154]	14	15,000 IU/kg PA	—	P. angio 37% at 12 hr	0
SK[111]	7	—	10,000–20,000 U/hr × 9–24 hr PA	P. angio 25% at 12–24 hr	29 (29)
		Heparin-0	Heparin 1000 U/hr†		
UK[188]	67	—	2000 IU/kg/hr × 24 hr PA		
		Heparin-0	Heparin—continuous‡	P. angio 26% at 30–48 hr	29 (14)
TPA[65]	36	—	25 mg × 2 hr IV ± 10 mg × 4 hr	P. angio 49% at 6 hr	20 (20)
TPA[192]	34	—	25 mg × 2 hr PA or IV then 10 mg × 5 hr PA or IV§	P. angio 38% at 7 hr Efficacy IP = IV	12 (12)
TPA[68]	22	—	50 mg × 2 hr IV	P. angio, marked/moderate improvement in 59% of patients at 2 hr	22 (22)

*The drug dosage used and results from several studies of thrombolytic drugs are shown. Different definitions for bleeding complications limit comparison among studies. Serious complications are considered those for which transfusion or surgical repair was needed. Total complications include "serious" bleeding and other episodes that necessitated stopping the thrombolytic infusion or caused a decrease in hematocrit of more than 10%. However, the total incidence of bleeding in the USPET study[189] did not separate major from minor bleeding; thus, its total incidence is disproportionately high. Some of the studies were performed in the 1970s and early 1980s, which might affect the willingness to transfuse blood. *Note:* The TPA study[68] referred to the percentage of patients with "marked/moderate" improvement rather than to the change in the pulmonary angiogram.

†Indicates heparin infusion titrated to a recalcification clotting time two to three times normal.

‡Indicates heparin infusion was adjusted to maintain partial thromboplastin time of 1.5 times normal.

§Heparin bolus 5000 U, then 1000 U/hr.

Abbreviations: IP = intrapulmonary; P. angio = pulmonary angiogram; PA = pulmonary artery infusion; SK = streptokinase; TPA = tissue plasminogen activator; UK = urokinase.

systemic fibrinolysis than urokinase or streptokinase. This agent binds more specifically to the plasminogen associated with fibrin in tissue clots, including surgical wounds, than to circulating fibrinogen. Clinical studies with TPA have shown that clots were effectively lysed but systemic fibrinolysis with decreased serum fibrinogen levels still occurred.[66, 68] Another study showed that TPA (80–90 mg over 6 hours) decreased RV size and ventricular septal shift in stable patients with PTE and pulmonary hypertension.[32]

A further study of TPA included 34 patients with 50% pulmonary vascular occlusion from PTE, 18 of whom were within 3 to 15 days of surgery.[192] Intravenous or intrapulmonary TPA (50 mg) was given over 2 hours and then another 50 mg was infused over 5 hours along with heparin. Heparin was used because animal studies have shown that it increases the efficacy of TPA.[23] PAP decreased from 31 to 12 or 18 mm Hg within 5 hours, and the severity of PTE determined from pulmonary angiograms declined by 38%. The extent of beneficial effect was similar whether TPA was administered through the pulmonary artery or intravenously. Bleeding complications, mainly at puncture or surgical sites, were present in 16 patients, including 5 of the postoperative patients.[192] The 12% incidence of major bleeding (transfusion of >2 U packed red blood cells) was similar to that seen in previously studied nonsurgical patients who were given thrombolytic therapy.[140]

A similar study of heparinized patients who received TPA doses of 40 to 80 mg over 40 minutes showed no angiographic improvement in 2 hours. Only slight, nonsignificant improvement was seen on $\dot{V}/\dot{Q}$ scans at 24 hours. One patient had serious gastrointestinal (GI) bleeding complications and later died.[30] TPA (0.6 mg/kg) was also given to fully heparinized, hemodynamically stable patients, with an average perfusion defect of 27%.[116] These patients had no bleeding complications and the perfusion defect decreased by 37% compared to 19% in those receiving only heparin.[116]

The efficacy of TPA (50 mg × 2 hrs) was compared prospectively to a 12-hour infusion of urokinase in nonheparinized patients.[68] Angiograms performed after 2 hours showed that 59% of the patients exhibited moderate or marked improvement following TPA compared to 13% of those given urokinase. PAP decreased by 2 hours after TPA but was unchanged after urokinase.[68] This rapid improvement may support the use of TPA for patients with severe hemodynamic compromise. The $\dot{V}/\dot{Q}$ scans at 24 hours demonstrated equal improvement in both groups.[68] Nine of 23 patients required early termination of urokinase because of "intolerable" bleeding and one was transfused. TPA was not discontinued because of bleeding but five patients required blood transfusions.[68]

Several case reports have described the successful use of thrombolytic therapy in hemodynamically compromised postsurgical patients. A 33-year-old woman with massive PTE 1 week after an abdominal hysterectomy received TPA (bolus of 10 mg and infusion of 90 mg over 2 hours) with dramatic improvement.[106] A 77-year-old woman with vaginal bleeding 2 days after a radioactive intrauterine implant deteriorated after massive PTE. She was not heparinized and received low-dose intrapulmonary streptokinase (10,000 U/h for 30 hours) through the angiographic catheter and survived.[139] TPA (100 mg over 2 or 3 hours) was used to treat two patients with severe hemodynamic compromise and relative contraindications to thrombolysis.[133] A young man, a paraplegic from a gunshot wound to the upper thoracic spine, suffered massive PTE 17 days after surgery. He developed shock that was resistant to aggressive support. TPA was given because his spinal injury was considered irreversible and it induced dramatic improvement. An elderly man, 2 weeks after a radical prostatectomy, presented with upper gastrointestinal hemorrhage and subsequently developed a PTE with hemodynamic compromise. TPA improved his hypotension and hypoxemia without increasing the GI bleeding.[133]

Thrombolytic therapy has also been successfully used in several pregnant patients. A 27-year-old woman with a 31-week pregnancy developed severe cyanosis and hypotension from PTE. A bolus of urokinase (200,000 IU) induced no improvement. Further deterioration occurred while she received heparin intravenously. Low-dose TPA (10 mg/h for 4.0 hours and then 2 mg/h for 1.5 hours) produced hemodynamic stability. A repeat pulmonary angiogram showed reperfusion of the right upper and middle lobes and partial reperfusion of the left lower lobe.[60] A 29-year-old woman who was 35 weeks pregnant and had a congenital antithrombin III deficiency developed severe dyspnea, hypoxemia, and pulmonary hypertension. A perfusion scan showed no flow to the right lung and hypoperfusion of the lower two thirds of the left lung. TPA (100 mg over 3 hours) resulted in almost complete reperfusion of the involved areas.[9] A standard dose of streptokinase was administered to a severely hypoxemic 19-year-old woman in her 28th week of pregnancy and improved her oxygenation.[46]

There is inadequate evidence to support the use of thrombolytic therapy in surgical patients. The risk/benefit ratio of thrombolysis in the postoperative period is unknown, since the incidence of serious or catastrophic bleeding after this therapy has never been analyzed in surgical patients. If a thrombolytic agent is selected for postsurgical patients, two regimens of short duration may be most appropriate because the number of complications correlated with the duration of treatment.[67] A bolus of urokinase (15,000 IU/kg)[154] allowed 12 of 14 patients to survive after life-threatening PTE. TPA (50 mg over 2 hours) was prospectively studied in 18 heparinized postoperative patients; a significant decline in pulmonary artery pressure with improvement in pulmonary angiogram was observed.[192] Conjoint administration of heparin and TPA has been studied more intensively than the combination of heparin and streptokinase[195] or urokinase. When the rate of hemodynamic response is critical and the patient is heparinized, TPA seems more appropriate than urokinase.

Pulmonary Embolectomy

Embolectomy is usually reserved for patients with greater than 55% to 60% of the pulmonary vasculature occluded.[48] Patients who develop shock following small or peripheral emboli should not undergo pulmonary embolectomy, because they have a high mortality rate with or without surgery.[49] Shock develops from small emboli when underlying cardiopulmonary pathology, such as chronic obstructive lung disease or coronary artery disease, leave minimal functional cardiopulmonary reserve.

Two thirds of the patients who initially develop hypotension following PTE die within the first 2 hours.[187] This rapid progression makes diagnosis and mobilization of a surgical team difficult. The appropriate patient population for surgical therapy is therefore difficult to define. Embolectomies clearly should not be performed in patients who would do well without the procedure. However, these procedures also should not be delayed until irreversible organ damage ensues. Candidates for embolectomy usually include unstable postsurgical patients who cannot receive thrombolytic therapy and patients who deteriorate within hours after the diagnosis is made, including those on thrombolytic therapy. Pulmonary embolectomies have been performed for PTE in the postpartum period.[163]

Recent mortality rates for embolectomy performed using cardiopulmonary bypass (CPB) ranged from 11% to 31%.[49, 70, 118] Higher mortality rates were seen in patients with shock from peripheral emboli or in those with chronic pulmonary hypertension, chronic medical diseases, or symptoms present for more than 7 days. Embolectomy studies with a higher proportion of postoperative patients, who tend to be younger and healthier than patients with chronic medical diseases, exhibit lower mortality rates.[48]

No multi-institutional studies have compared thrombolysis with embolectomy. Two older retrospective studies concluded that survival after thrombolytic therapy was equal to or better than that following embolectomy.[131, 168] A Danish study prospectively compared streptokinase and pulmonary embolectomy. Patients (n = 28) with 30% to 55% of the pulmonary artery obstructed received streptokinase, and those (n = 25) with 55% to 75% occlusion of the pulmonary artery or with contraindications to streptokinase underwent an embolectomy.[118] Hospital mortality rates were 21% in the streptokinase group and 20% in the embolectomy group, which included more hemodynamically compromised patients. Seven of the 25 embolectomy patients came to the operating room in cardiac arrest, and four of these survived. Patients without cardiac arrest had an 11% in-hospital mortality rate after embolectomy.[118] The good results in the embolectomy group are probably attributable to the inclusion of many otherwise healthy, postoperative patients.

Pulmonary embolectomy using CPB has a much lower mortality than the classic Trendelenburg procedure, which employs normothermic cardiac arrest and outflow occlusion of the pulmonary artery.[49] "Inflow" occlusion of the inferior and superior venae cavae has more recently been used to perform pulmonary embolectomies. The mortality rate was high (74%) in patients who suffered a cardiac arrest before coming to the operating room but was 20% in those with systolic pressures less than 100 mm Hg and no arrest. Clarke-Pearson et al [28] supported use of inflow occlusion when CPB capability was not available.[27]

Anesthetic Management for Pulmonary Embolectomy

An emergency embolectomy is performed only when severe hemodynamic compromise is present and usually when thrombolysis is contraindicated or has failed. The patient is typically hypoxemic, hypotensive, or even in full cardiac arrest. The induction of anesthesia in unintubated patients may be associated with cardiovascular collapse. Surgeons believe that preoperative use of partial femoral arteriovenous CPB is a major reason that survival has increased after pulmonary embolectomy.[123, 167, 186] Inserting partial CPB with local anesthesia has therefore been strongly encouraged in patients with cardiogenic shock from PTE. Cardiac arrest during anesthetic induction has been reported in surgical series published as recently as the 1980s but the anesthetic techniques were not described.[16, 167]

Anesthetic goals during pulmonary embolectomy are (1) to avoid drugs with negative inotropic or systemic vasodilatory effects, (2) to maintain the RV preload (CVP) high, but not too high, (3) to lower the pulmonary vascular resistance without increasing the intrapulmonary shunt fraction or decreasing systemic vascular resistance, and (4) to keep the heart rate relatively high because stroke volume may be low or fixed.

Patients with acute PTE are extremely sensitive to drugs with vasodilating and negative inotropic properties. Initially, only amnestic drugs (scopolamine or low-dose benzodiazepines) may be tolerated; later, small titrated doses of narcotics and possibly extremely low concentrations of inhalation agents can be used. Based on studies in patients with other types of critical illnesses, diazepam, narcotics, or etomidate are preferable to sodium thiopental or midazolam, which can induce vasodilation or myocardial depression.[100] It is not known if ketamine or nitrous oxide aggravates the pulmonary hypertension caused by PTE, but these drugs may increase the PAP in other diseases with pulmonary hypertension. Nitrous oxide is not a good choice in any event, because of the severe hypoxemia resulting from massive PTE.

As discussed earlier, the CVP, not the PCWP, must be used as the endpoint for volume administration. The use of specific inotropes has already been discussed. Norepinephrine may be especially useful for increasing RV coronary perfusion pressure. A pulmonary artery catheter provides useful information, but its placement should not delay the surgery. Pulmonary artery catheter insertion may be more likely than usual to cause arrhythmias in these patients with severe RV ischemia. A Swan-Ganz catheter could also, theoretically, dislodge RV thrombi and induce hemodynamic deterioration.[100] Right atrial or ventricular emboli "in-transit" are relatively rare, but the increased prevalence of echocardiography has led to more awareness of this phenomenon.[58, 104] Hyperventilation with small frequent breaths may be useful before cardiopulmonary bypass, since respiratory alkalosis functions as a nonspecific pulmonary vasodilator in other types of pulmonary hypertension.[55] The necessary minute ventilation will be higher than expected, because of the large dead space induced by the embolism. Hypoxic pulmonary vasoconstriction in dogs embolized with blood clots has also been shown to be more effectively preserved when P_{CO_2} was 30 mm Hg than when it was 42 mm Hg.[59] Along with their negative inotropic effects, inhalational anesthetics may inhibit hypoxic pulmonary vasoconstriction.[52] However, patients undergoing routine thoracotomy with intravenous anesthetics and double-lumen endobronchial tubes did not exhibit altered Pa_{O_2} when 1 MAC of isoflurane or halothane was added to the inspired gas mixture.[161] Positive-pressure ventilation or "sighs" can facilitate retrieval of thrombi from the pulmonary arteries by moving embolic fragments into the more proximal vessels.[113]

Patients undergoing pulmonary embolectomy are frequently at a high risk of hemorrhage owing to prior administration of heparin or thrombolytic agents; thus adequate venous access is needed. Fresh frozen plasma or cryoprecipitate may be required to increase fibrinogen levels after the embolectomy in patients who have received thrombolytic therapy. Massive pulmonary bleeding may rarely occur as a result of pulmonary infarction (ischemia) and reperfusion following embolectomy for acute PTE.[119] Application of PEEP may decrease the bleeding but this complication is nearly always fatal.[113]

Transvenous Catheter Embolectomy

Greenfield designed a steerable catheter with a suction cup that can be used to remove central PTE in a procedure that is less invasive than a thoractomy.[71] The suction cup is inserted into a femoral or jugular vein under local anesthesia. The mortality rate is, nevertheless, 27% in these very unstable patients.[71] Femoral arteriovenous CPB may be initiated to maintain hemodynamic stability during the procedure, but the heart must remain beating. Anesthesiologists providing monitored anesthesia care for these critically ill patients must consider the risk of bleeding from percutaneous punctures or cutdowns in anticoagulated patients, intrapulmonary bleeding from reperfusion of the lungs, ventricular arrhythmias, bradycardia, and perforation of the pulmonary artery.[64]

Inferior Vena Cava Procedures

Lower extremity thrombi can be prevented from embolizing to the lung by partially or fully occluding the inferior vena cava (IVC). This procedure is done through a laparotomy; however, a partially occluding filter can also be placed in the IVC using a noninvasive transvenous approach. Indications for partial IVC occlusion include contraindications to, or complications from, anticoagulants; recurrent PTE; and less commonly, to prevent embolization of DVT. Ligation of the IVC is indicated for septic or paradoxical emboli.[102] The intra-abdominal approach to the IVC is associated with a mortality rate of 5% to 30%. Severe hypotension develops in 2% of patients when the IVC is ligated.[14, 102] These hypovolemic patients require fluid administration and treatment with inotropes. Chronic venous insufficiency of the lower extremities is a serious and relatively common complication of the transabdominal procedure.

The Greenfield vena cava filter can be placed through a femoral or jugular vein under local anesthesia. Mortality following filter placement is rare,[71, 98, 162] and venous insufficiency occurs less often with the Greenfield filter than following IVC ligation or partial occlusion.[102] A large retrospective study of the Greenfield filter demonstrated that fatal PTE occurred in 1.5%, occlusion of the IVC in 4.5%, and chronic phlebitic syndrome in 3% of patients.[162] Greenfield cautions that acute occlusion of the IVC filter by a dislodged thrombus can be misinterpreted as recurrent PTE and mistakenly treated with inotropes instead of the fluid resuscitation needed to improve the impaired venous return.[71] A retrospective study showed that heparin therapy did not improve outcome following placement of Greenfield filters.[94]

INTRAOPERATIVE PRESENTATION OF PTE

Intraoperative PTE may be difficult to distinguish from other causes of acute hemodynamic deterioration, such as myocardial ischemia, arrhythmias, or unrecognized hypovolemia. Intraoperatively, this complication occurs most commonly in older or immobilized patients who have cancer or traumatic injuries.[48] PTE may occur after tourniquet inflation or deflation, manipulation of the leg, or change in patient position.[56, 126] Typical signs and symptoms of PTE in anesthetized patients include cyanosis, hypoxemia, hypotension, neck vein distension, wheezing, decreased pulmonary compliance, decreased end-tidal CO_2, increased $PaCO_2$, pulmonary hypertension, increased CVP, and normal PCWP. The decrease in end-tidal CO_2 is not specific and results from ventilation of unperfused alveoli combined with decreased cardiac output and pulmonary blood flow. Intraoperative diagnosis may be made by angiography through the Swan-Ganz catheter.[10] Caution must be used, since large boluses of dye may have a pulmonary hypertensive and negative inotropic effect. Heparin administration induced hemodynamic and symptomatic improvement in two patients with intraoperative PTE.[10, 120] As previously discussed, heparin prevents the ongoing release of vasoactive and bronchoconstrictive mediators from platelets and thrombin and may improve oxygenation and the circulatory status. Adequate cardiopulmonary resuscitation did not always prevent death. Pulmonary embolectomies, with or without CPB, have been, at times, successful.[48, 56, 78] A Trendelenburg procedure or inflow occlusion technique may be attempted after an intraoperative PTE if CPB is not available (see previous discussion).

A 63-year-old woman who was undergoing a total knee arthroplasty developed a cardiac arrest from PTE and was placed on partial femoral CPB because of severe, resistant hypotension. PTE was diagnosed by transesophageal echocardiography and a portable technetium scan. She was given TPA (100 mg) by a pulmonary artery catheter. Her hemodynamic status subsequently improved, but she died from anoxic encephalopathy.[126]

EFFECT OF ANESTHETIC TECHNIQUE ON DVT

Anesthetic management affects the incidence of DVT. Regional anesthesia tends to decrease the incidence of DVT in high-risk patients. Epidural anesthesia has been associated with a lower incidence of DVT than general anesthesia in patients undergoing hip arthroplasty when analgesia was maintained into the postoperative period.[135] The incidence of both distal and proximal DVT was also lower with epidural compared with general anesthesia in patients undergoing total knee replacement.[95, 173, 174] Modig[134] attributes this effect to greater lower extremity blood flow and to the local anesthetic, which inhibits platelet aggregation, has fibrinolytic properties, and protects the vascular endothelium. Spinal anesthesia has also been shown to decrease the incidence of DVT in patients undergoing open prostatectomy[79] or hip surgery.[45] However, a recent review emphasized that neither epidural nor spinal anesthesia was as effective as other means of prophylaxis for hip surgery patients.[159] DVT developed in 60% to 70% of untreated patients receiving general anesthesia, in 30% to 40% of those receiving regional anesthesia, and in only 5% to 20% of patients receiving general anesthesia and DVT prophylaxis with low molecular weight heparin or heparin with dihydroergotamine.[159]

Prophylactic administration of heparin may affect the decision to perform regional anesthesia. Authorities do not recommend spinal anesthesia after low-dose heparin for DVT prophylaxis.[89, 138, 181] However, epidural anesthesia has been used safely in several large series of patients receiving preoperative low-dose heparin or oral anticoagulants.[3, 61, 143] No neurologic complications or epidural hematomas were reported in two recent reviews of the subject.[147, 182] Only recently have epidural hematomas been reported in patients receiving prophylactic heparin. A 54-year-old woman with obstructive jaundice from common bile duct carcinoma was receiving subcutaneous heparin (5000 U every 12 hours). A thoracic epidural catheter was placed before surgery for postoperative analgesia. The expected incomplete motor block of the legs developed after bupivacaine 0.375% every 4 hours. Complete paraplegia below the level of T11–12 was noted on the first postoperative day. Subcutaneous heparin and bupivacaine were discontinued on the second postoperative day. Decompressive laminectomy on the third postoperative day did not improve neurologic function. The patient's preoperative and postoperative thrombin times were 17 seconds (normal, 7–12 seconds). Prothrombin and partial thromboplastin times were not reported before surgery and were normal after surgery despite the obstructive jaundice.[47, 130]

A 75-year-old man with rectal carcinoma and normal clotting studies was receiving heparin, 5000 U every 12 hours. A lumbar epidural catheter was placed for analgesia after a colostomy was performed. Blood was obtained during catheter insertion; therefore, no local anesthetic was injected. Severe back pain and complete paraplegia developed over the next 3 hours. The paralysis persisted despite early diagnosis and decompressive laminectomy for the epidural hematoma.[44]

A careful individual decision needs to be made about whether an epidural catheter should be placed or maintained in patients receiving subcutaneous heparin. It is important to realize that some patients have abnormal clotting studies after "standard" low-dose heparin. The partial thromboplastin time was 1.5 times normal in 15% of general and gynecologic surgical patients 2 to 4 hours after a preoperative 5000-U dose of heparin.[29, 74] The activated clotting time also increased by 10 seconds for as long as 5 hours.[29] Full anticoagulation resulted from this standard heparin dose in 1% to 2% of patients.[63, 74] The risk of an epidural hematoma is extremely low, and there are demonstrated benefits from postoperative epidural analgesia, including a decreased incidence of DVT. The difficult decision about whether to place an epidural catheter in any patient receiving subcutaneous heparin should be influenced by the clotting time in order to eliminate those who are sensitive to the agent.

CHRONIC PULMONARY THROMBOEMBOLI

A small percentage of patients with untreated or recurrent PTE develop chronic pulmonary hypertension and cor pulmonale.[125, 137, 151] Pulmonary embolectomies to remove chronic PTE have been successfully performed with CPB.[41] Surgical candidates have pulmonary vascular resistances greater than 300 dynes/sec/cm^5, central emboli, and dyspnea with exercise. Hospital mortality rates of 12.6% have been reported following embolectomy in debilitated patients with chronic PTE.[41] Extreme hypothermia, ample cardioplegia, a cooling jacket on both ventricles, and intermittent circulatory arrest to minimize backbleeding from hyperplastic bronchial arteries were used. Ventilator dependency for more than 5 days was predicted by prolonged CPB, ascites, or transfusion of more than 4 U of blood.[40] Postoperative problems included airway hemorrhage and reperfusion pulmonary edema.[40, 41] New perfusion defects have also been recognized in the postoperative period after embolectomy for chronic PTE. These defects are not embolic but are believed to result from pulmonary vascular "steal," with redistribution of pulmonary arterial resistance following the thromboendarterectomy.[144]

SUMMARY

Anesthesiologists should be aware preoperatively of which patients are prone to thrombosis in order to assess the risk factors and possible need for DVT prophylaxis or to diagnose existing DVT. Knowledge of the nonspecific cardiopulmonary symptoms of PTE is necessary for early diagnosis. Heparin anticoagulation is standard treatment. Thrombolytic therapy is not recommended in the first 10 days after surgery. Inferior vena cava filters should be placed in patients with contraindications to anticoagulation. Massive, catastrophic PTE requires intensive hemodynamic support and difficult decisions may be required for definitive management. Several large series have reported good outcomes from pulmonary embolectomy in surgical patients suffering massive PTE (>55%–60% obstruction). However, selecting patients appropriate for pulmonary embolectomy is an extremely difficult decision.

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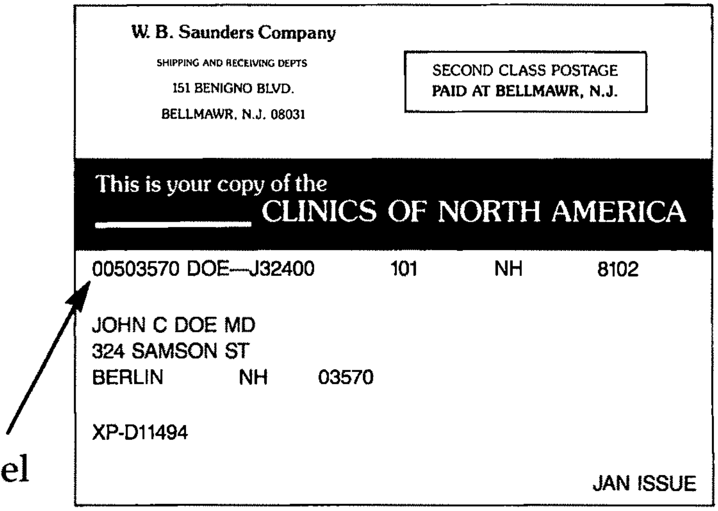

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